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# MODELLING AND QUANTIFYING BRAIN CONNECTIVITY AND DYNAMICS WITH APPLICATIONS IN AGING AND ADHD

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# Modelling and quantifying brain connectivity and dynamics with applications in aging and ADHD
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By


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To my family.

# ABSTRACT

Human brain is a complex organ and made up of integrative networks encompassing a large number of regions. These regions communicate with each other to share information involved in complex cognitive processes. Functional connectivity (FC) represents the level of synchronization between different brain regions/networks. Studying functional interactions of the brain creates a platform for understanding functional architecture of the brain as an integrative network and has implications for understanding human cognition. Furthermore, there is evidence that FC patterns are sensitive to different diseases. In addition, age is a significant determinant of intra-/inter-individual variability in the FC patterns. Therefore, key aims for the studies included in this thesis were to apply and develop novel resting-state FC methodologies, with applications in healthy aging and ADHD. Indeed, measures of the brain's FC may serve as a useful tool to diagnose and predict the course of disease, and useful in developing individualized therapies.

Age- or disease-related alterations in the FC could reflect a multitude of factors, including changes in structural connectivity. However, we still have limited knowledge of the emergence of brain dynamics from the underlying anatomy. The interplay between the brain's structure and dynamics underlies all brain functions. Therefore, in the last study we focused on the systematic modeling of the brain network dynamics. Large-scale computational models are uniquely suited to address difficult questions related to the role of brain's structural network in shaping functional interactions. In addition, computational modeling of the brain enables us to test different hypotheses without any experimental complication while it provides us with a platform for improving our understanding of different brain mechanisms. A new macroscopic computational model of the brain oscillations for resting-state fMRI was introduced in this thesis, which outperforms previous model in the same class. Then, the effects of malfunctions in different brain regions were simulated and subsequently predicted perturbation patterns were recruited for local vulnerability mapping as well as quantification of hazard rates induced after perturbing any brain region.

# LIST OF SCIENTIFIC PAPERS

I. Salami A, Wåhlin A, **Kaboodvand N**, Lundquist A, Nyberg L, 2016. Longitudinal evidence for dissociation of anterior and posterior MTL resting-state connectivity in aging: Links to perfusion and memory. Cerebral Cortex. 26(10):3953-3963. doi: 10.1093/cercor/bhw233.

II. **Kaboodvand N**, Bäckman L, Nyberg L, Salami A, 2018. The retrosplenial cortex: A memory gateway between the cortical default mode network and the medial temporal lobe. Human Brain Mapping. doi: 10.1002/hbm.23983.

III. **Kaboodvand N**, Iravani B, Fransson P, 2019. Synergetic configurations of dynamic functional connectivity patterns in ADHD. Manuscript on bioRxiv. doi: 10.1101/734111.

IV. **Kaboodvand N**, van den Huevel M, Fransson P, 2019. Adaptive frequency-based modeling of whole-brain oscillations: Predicting regional vulnerability and hazardousness rates. Network Neuroscience. doi: 10.1162/netn_a_00104.

# LIST OF ADDITIONAL SCIENTIFIC PAPERS NOT INCLUDED IN THE THESIS

I. Nyberg L, Karalija N, Salami A, Andersson M, Wåhlin A, **Kaboodvand N**, Köhncke Y, Axelsson J, Rieckmann A, Papenberg G, Garrett DD, Riklund K, Lövdén M, Lindenberger U, Bäckman L, 2016. Dopamine D2 receptor availability is linked to hippocampal-caudate functional connectivity and episodic memory. Proceedings of the National Academy of Sciences of the United States of America. 113(28):7918-23. doi: 10.1073/pnas.1606309113.

II. Iravani B, **Kaboodvand N**, Arshamian A, Fransson P, 2019. Different neural dynamics and multiple pathways to ADHD: A Simulation of ADHD brain dynamics and therapeutic effect of nodal excitatory. (In manuscript)

# CONTENTS

# CASES LIST OF ABBREVIATIONS

# 1 CHAPTER 1: PERSONAL INTRODUCTION

Growing up in a big family surrounded by different characteristics and various ways of thinking taught me that heterogeneity is an essential element of community success and an integrated community benefits a lot from all the interactions within the group and the communications with the other communities. Through my lifetime experiences I realized how the entity and function of a community depends upon its interactions at multiple spatial and temporal scales, and dealing with inevitable dynamic re-organizations.

Acquiring a wide range of general information and the rich experience in group integration were among the many advantages arising from the heterogeneity and information transfer in our community. With all the advantages of being a member of a big group, I also had experiences of observing the failures and perturbations applied to our community, or its neighbor communities and higher-level networks. I learned how a synergetic network is capable to find a way of coping with unavoidable life incidents, highlighting the necessity of having network dynamics.

With all that being said, I believe that my academic background in network science goes back to high school, when I was introduced with the fascinating world of network theory in a course called "discrete mathematics". I found the beauty of network theory in its capability to address a broad range of questions and the wide range of applications while exhibiting maximum parsimony. Then, I got fascinated with exploring the most complicated network in the known universe, the brain. Understanding the interactions in the complex brain network can be a double-edged sword. Not only will it help us get the hang of brain development and aging, brain disorders, and complex cognitive processes, with potential therapy implications, but also to shed light on engineering efficient and robust social and artificial networks.

Later, I was introduced to mathematical modeling of biological systems and nonlinear dynamics, during two fascinating inter-related courses given by prof. Farzad Towhidkhah and prof. Mohammad Reza Hashemi Golpayegani, namely "System Identification" and "Electrophysiology". Mathematical modeling is the art of describing real-world systems by tractable mathematical language, providing a platform for theoretical analysis to get insights into fundamental mechanisms and relationships. And nonlinear dynamics is an amazing concept in mathematics that helps us to understand some of the wonders of the nonlinear dynamic world.

This thesis grows from my abiding interest in network science and mathematical modeling and combining them for a better understanding of human brain as the most known complex system in the world.

# 2 CHAPTER 2: MAPPING FUNCTIONAL ARCHITECTURE OF THE BRAIN

*"The brain is similar to an orchestra. It has sections like the strings or percussion. But one cannot just look at it in that way. An orchestra is much more than its sections, they all need to come together to produce music."*

*— Marcus E. Raichle*

Understanding the functional architecture of the human brain is an increasingly attractive topic in neuroscience. Human brain is a complex organ and made up of integrative networks encompassing a large number of regions. These regions communicate with each other to share information involved in complex cognitive processes. Temporal dependency between neuronal activities of different brain regions is known as functional connectivity (FC). Investigation of the FC in the brain has been facilitated by recent advances in the functional neuroimaging techniques, in terms of both acquisition and analysis of the brain activity data.

## 2.1 FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI)

Researchers have been fascinated by brain activity for a long time. The first documented case of measuring the change in the blood flow in relation to the brain activity goes back to the 19th century, when an Italian physiologist (Angelo Mosso) recorded the pulsation of the human cortex in patients with skull defects. He concluded that mental activity causes an increase in brain blood flow. His research was a forerunner of the functional neuroimaging techniques like functional magnetic resonance imaging (fMRI). The fMRI methodology relies on the tight coupling between blood oxygenation and neuronal activation (Bandettini, 2009), such that areas with more blood flow have greater neuronal activity. The fMRI data are comprised of thousands of voxels exhibiting blood-oxygen-level dependent (BOLD) signals, and is an indirect, but fairly accurate, measure of neuronal activity (Figure 1).

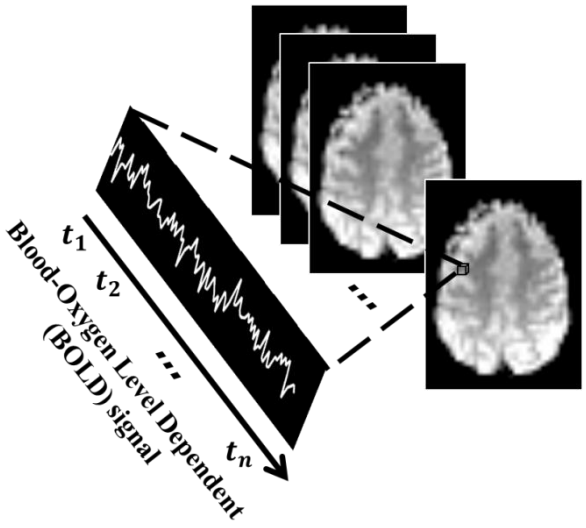


*Figure 1. Example fMRI data.*

The association between the BOLD signals and the underlying neuronal activity is not clear. However, a previous science paper (Mukamel *et al.*, 2005) provided some evidence that fMRI BOLD signals can provide a reliable measure of the neuronal firing rates. In particular, fMRI with a very high spatial and relatively good temporal resolution has received interest in the brain-imaging literature, allowing researchers to safely and non-invasively map neural-activity changes while participants are either resting or performing a cognitive task.

### 2.1.1 Resting-state versus Task-based Experiments

*"The brain apparently uses most of its energy for functions unaccounted for—dark energy, in astronomical terms."*

*— Marcus E. Raichle*

Most of our knowledge about brain function comes from task-related fMRI experiments during which subjects perform a cognitive task (e.g. an episodic memory task). It should be noted that, task-based fMRI studies are commonly analyzed based on linear superposition theory, which is a reductionistic approach. The linear superposition theory claims that intrinsic activity and task evoked activity linearly sum together to procedure the observed signals. However, previous literature (Bolt *et al.*, 2018; Huang *et al.*, 2017), suggests that there is a functional interdependence between them. Hence, separation of intrinsic and task-evoked activity based on linear superposition is false, or at least not universal (Bolt *et al.*, 2018).

Furthermore, task-related fMRI may not inform us about spontaneous neuronal activity during resting state which is intrinsically generated by the brain. This is a serious omission, because the resting brain consumes a substantial portion of the body's energy, but only accounts for 2% of the body mass. Interestingly, task-evoked increases in energy-consumption are less than 5%, compared with baseline energy consumption (Fox and Raichle, 2007). As Fox and Raichle stated: "If we hope to understand how the brain operates, we must take into account the component that consumes most of the brain's energy: spontaneous neuronal activity" (Fox and Raichle, 2007). Moreover, we note that the brain's intrinsic activity is not random noise, but it exhibits specific spatial and temporal organization across the whole brain (Biswal *et al.*, 1995; Fox and Raichle, 2007; Fransson, 2005). These spontaneous fluctuations continue throughout task paradigms and contribute to inter-trial variation in BOLD activity as well as behavior (Fox and Raichle, 2007).

Therefore, resting state fMRI has received growing attention during the last two decades. This functional imaging technique provides a powerful tool to map the functional architecture of the brain by measuring interactions among different brain regions while a person is not performing a specific task (Biswal *et al.*, 1995). Findings from resting-state fMRI posit a new view on brain function, based on which the brain is not idle at rest (Ingvar, 1979). Rather, low frequency (i.e., at or below 0.1 Hz) fluctuations of the BOLD signal, conceptualized as either endogenous oscillations or spontaneous neural activity, is pervasive and consume a major portion of the brain's energy (Raichle, 2006).

The amount of available resting-state data has been exploded because of several advantages that it has, such as being very simple and less susceptible to task-related compliance and not being confounded by task performance, effort, practice effects, etc. Besides, it takes away the difficulties of experimental design, subject compliance and training requirements, making it an appropriate choice for a broad range of developmental and clinical studies like older adults and sedated patients with brain injury (Ombao *et al.*, 2016). Also, less movement artifacts are expected. Furthermore, a brief fMRI (e.g. 6 min) resting-state session is sufficient to explore diverse brain systems and interactions among systems. By measuring the level of co-activation between BOLD signals extracted from distal brain regions, we are able to estimate FC between those regions. Resting-state studies have found large-scale spatial patterns of coherent signals, which are corresponding to functionally relevant systems reflecting the neuronal baseline activity supporting fundamental processes in relation to perception and cognition. In other words, brain regions with similar functionality which cooperate during active tasks, are also functionally connected to each other during resting-state.

Indeed, low frequency fluctuations of the BOLD signal are often synchronized in a hierarchy of functional brain networks spanning different brain-circuits (Biswal *et al.*, 1995). These resting-state networks (RSNs) have showed a high degree of consistently both across groups of subjects (including for example, monkeys (Vincent *et al.*, 2007) and infants (Fransson *et al.*, 2007)) and in repeated sessions on the same subject, exhibiting significant temporal dynamics (Damoiseaux *et al.*, 2006; van de Ven *et al.*, 2004). The RSNs in the adult human brain are including but not limited to visual, somatosensory and attention networks, as well as the default mode network (DMN). Yet despite the gross similarities, resting-state functional connectivity analyses have revealed inter-subject variability in the intrinsic organization of the brain predicting individual differences in cognitive domains and age (Almgren et al., 2018; Geerligs et al., 2015b; Mueller et al., 2013; van den Heuvel et al., 2009).

The brain's functional architecture is remarkably preserved across different mental states as well (Calhoun *et al.*, 2008; Cole *et al.*, 2014; Smith *et al.*, 2009), albeit with significant state-dependent temporal and spatial modulation of the RSNs and their related FC patterns (Arbabshirani et al., 2013; Calhoun et al., 2008; Cole et al., 2014; Geerligs et al., 2015b). Despite the fact that FC patterns are to some degree state-dependent, the underlying intrinsic functional organization during resting-state may still act as a functional fingerprint (Dubois, 2016; Finn *et al.*, 2015). In more detail, previous research suggests that RSNs are able to discriminate individuals, indicating the potential use of FC as a stable, trait-like measure to draw inferences about single subjects (Finn *et al.*, 2015).

## 2.2 THE DEFAULT MODE NETWORK

*"A baseline or control state is fundamental to the understanding of most complex systems."*

*— Marcus E. Raichle*

The DMN was originally identified in a meta-analysis of task-induced deactivations in positron emission tomography (PET) data (Shulman *et al.*, 1997), however the explication of

the DMN is associated with a seminal study by Raichle and collegues (2001), who found the same set of brain regions being consistently deactivated while subjects were involved in cognitive demanding tasks. Findings from resting-state FC analyses revealed information about the functional architecture of the DMN (Buckner *et al.*, 2008; Fransson, 2005). The DMN consists of multiple dynamically coupled and widely distributed subsystems (Andrews-Hanna *et al.*, 2010; Buckner *et al.*, 2008; Raichle *et al.*, 2001; Salami *et al.*, 2016). One of the core DMN subsystems encompasses the posterior cingulate cortex (PCC) and the retrosplenial cortex (RSC) (Buckner *et al.*, 2008; Fransson and Marrelec, 2008; Fransson, 2005), often jointly referred to as posteromedial cortex. There are also other DMN regions located in the lateral parietal and medial prefrontal cortices. In addition, a medial temporal lobe (MTL) subsystem, including hippocampus and adjacent structures, is distinct from, yet related to, the major cortical DMN regions (Andrews-Hanna *et al.*, 2010; Buckner *et al.*, 2008; Salami *et al.*, 2016). The DMN, particularly the posteromedial cortex, shows high neural activity when an individual is nominally at rest— lying still in the scanner— or is retrieving an autobiographical memory ("What did I have for lunch?") (Foster and Parvizi, 2012). In addition, the aforementioned network may show decreased activation during attention-demanding tasks compared to the baseline conditions (Buckner *et al.*, 2008; Fox *et al.*, 2005; Fransson, 2005). Interestingly, the DMN consumes more energy than any other network in the brain (Raichle and Snyder, 2007). The exact function of the DMN is still unclear, however; DMN activity has been associated with different cognitive domains (e.g., episodic memory, self-referential processing, mind wandering) (Buckner *et al.*, 2008). Indeed, there are two key hypotheses for DMN function. The first proposal suggests that the DMN underlies autobiographical memory and self-referential thoughts related to either the past or the future (Buckner and Carroll, 2007; Buckner *et al.*, 2008; Holland and Kensinger, 2010; Spreng and Grady, 2010). Each DMN subsystem underlying a specific task (e.g. autobiographical memory, emotional and self-referential social thoughts) is integrated through the act of a particular DMN hub and the subsystems are ultimately interlinked through the action of DMN "hubs" (Buckner *et al.*, 2008). The second proposal suggests that the DMN acts to focus our attention in a broad sense (Gusnard *et al.*, 2001; Raichle *et al.*, 2001; Scheibner *et al.*, 2017), such that goal-directed tasks requiring deliberate allocation of attentional resources, result in suppression of DMN activity (especially in posterior DMN hubs).

Abnormalities in intrinsic FC within the DMN have been related to almost all major psychiatric disorders including dementia, schizophrenia, epilepsy, anxiety, depression, chronic pain, obsessional disorders, autism, attention deficit hyperactivity disorder (ADHD) (Broyd *et al.*, 2009; Buckner *et al.*, 2008; Menon, 2011). Particularly, there is a body of evidence that the DMN exhibits abnormal activity and connectivity patterns in patients with ADHD compared to healthy controls. Notably, there is an overall decrease in the DMN coherence in ADHD (Castellanos *et al.*, 2008; Uddin *et al.*, 2008), with particularly reduced FC between the precuneus and other DMN subsystems (Castellanos *et al.*, 2008; Uddin *et al.*, 2008). Additionally, an increasing bulk of evidence suggests age-related alterations in FC

within the DMN (Andrews-Hanna *et al.*, 2007; Damoiseaux, 2017; Ferreira and Busatto, 2013; Spreng *et al.*, 2016). Critically, age-related DMN alterations have been linked to cognitive impairment in old age (Andrews-Hanna et al., 2007; Greicius et al., 2004; Salami et al., 2016, 2014; Wang et al., 2010).

Taken together, understanding the DMN's functional architecture and its alterations across different conditions have important implications for cognitive impairment in aging and disease. The chief aims of the first conducted studies were to further investigate alterations of the DMN using new methods for resting-state FC analysis, and to elucidate how individual differences in DMN connectivity is linked to cognition, age and ADHD.

## 2.3 METHODOLOGY

### 2.3.1 Preprocessing of the fMRI Data

*"A better world won't come about simply because we use data; data has its dark underside."*

*— Mike Loukide*

Analyses of resting-state data is a relatively challenging task. Resting-state fMRI is affected by several factors, such as variability across time within individuals (Poldrack *et al.*, 2011) and artifacts caused by head movement (Poldrack et al., 2011; Van Dijk et al., 2012). It is thus essential to perform different pre-processing operations on fMRI data and to correct for potentially confounding artifacts, as well as prepare the data for later processing stages. There is a standard fMRI pre-processing pipeline that is widely used. The standard pipeline includes:

- Detecting and correcting scanner artifacts (e.g. spikes and ghosting).
- Slice-timing correction to compensate for differences in the acquisition of slices in the image.
- Realignment of scans across time by rigidly aligning each volume to the first image volume (also known as motion correction).
- Co-registration of fMRI data to T1-weighted images using within-subject rigid registration.
- Segmentation of T1-weighted images into gray matter (GM) and white matter (WM).
- Spatial normalization into Montreal Neurological Institute (MNI) template space and smoothing by a Gaussian kernel.
- Removing nuisance and motion-related regressors.
- Temporal band-pass filtering to remove non-neural fluctuations of the BOLD signal.

This pipeline is widely used in the literature. However, these steps are not all necessary. For example, the fMRI data which is acquired for neurosurgical planning does not require any normalization or spatial smoothing. In addition, there is considerable amount of discussion on how to effectively remove the nuisance signals. One of the most popular methods is anatomical component based noise correction, namely CompCor (Behzadi *et al.*, 2007). This

technique uses noise-related principal components estimated from the WM and cerebrospinal fluid (CSF) voxels. Compared with averaging across WM and CSF voxels, CompCor may provide a better proxy for nuisance signals from WM and CSF (Chai *et al.*, 2012; Parkes *et al.*, 2018). This method does not however eliminate the need for global signal regression (Liu *et al.*, 2018; Murphy and Fox, 2017; Parkes *et al.*, 2018). Global signal regression removes the average signal extracted from the whole brain and may eliminate non-neuronal sources. There is some evidence that fluctuations in arousal contribute to this global signal and, for example, caffeine intake modulates this signal. Therefore, avoiding global signal regression may provide more precise results in circadian studies (Power *et al.*, 2017). Global signal regression needs to be performed with additional care for comparing cohorts with dissimilar noise characteristics, for example in comparison of schizophrenic versus healthy controls (Murphy and Fox, 2017; Nalci *et al.*, 2017).

Resting-state functional and structural MRI data were here preprocessed using the Statistical Parametric Mapping software (SPM12; Welcome Department of Cognitive Neurology, University College London, London, United Kingdom). Using computational methods, the preprocessed data can be subsequently analyzed using various approaches, among which the most common methods are described below.

### 2.3.2 Functional Connectivity Metrics

*"All mass is interaction."*

*— Richard Feynman*

Studying functional relationships between different brain regions has been one of the main aims of functional neuroimaging. FC is defined as the undirected association between signals from two different brain regions, with no assumptions about the underlying biology. Although, we can quantify FC based on both linear (temporal correlation, spectral coherence) and nonlinear (mutual information, phase synchronization) measures of synchronization (Quian Quiroga *et al.*, 2002), the Pearson correlation coefficient is the most commonly used measure of resting-state FC.

Back in 2005, Biswal used correlation between time-courses of low frequency (< 0.1 Hz) fluctuations, arising from changes in blood oxygenation flow, for mapping the functional connectivity patterns of the brain at rest (Biswal *et al.*, 1995). The idea of using correlation function to estimate the functional relationships between brain regions goes back to nineteenth century, using electroencephalogram (EEG) signals (Shaw, 1984). Afterwards, the seed-based correlation approach has been one of the most widely adopted analytical techniques for studying the cross-talk between distal brain regions (Biswal *et al.*, 1995; Fox *et al.*, 2005; Fransson, 2005; Fransson *et al.*, 2011; Nyberg *et al.*, 2016). This is often carried out by predefining a seed region of interest (ROI), based on a priori hypothesis. Then, the correlation between the BOLD signal extracted from the seed ROI and BOLD signals in all other voxels of the brain is computed. It is based on the assumption that voxels with similar neuronal activity will change proportionally. As a result, a connectivity map is obtained,

representing brain regions strongly correlated with the predefined ROI. In order to compute the signal of the predefined ROI, one may simply average the signals across all voxels within the ROI (Biswal *et al.*, 1995; Fox and Raichle, 2007; Fransson, 2005). However, it has rather been suggested to use the first eigenvariate of the ROI instead of the average signal (Poldrack *et al.*, 2011).

Coherence, that is the spectral representation of correlation in the frequency domain, has been another suggested function for computing the FC (He *et al.*, 2007; Li *et al.*, 2009), although it may be considered of less interest for the low frequency fluctuations as observed in resting-state fMRI data. Coherence captures the relationships either based on change in power or change in phase, which makes the interpretation of relationships more difficult. Furthermore, coherence only captures the stability of the relationship between two signals, rather than providing direct information on their relationship (Sakkalis and Zervakis, 2009).

Usually, FC is calculated over an entire scan, as one averaged measure of inter-regional neural interaction, referred to as "static connectivity". However, previous studies have revealed that investigation of interactions at different frames of neural signals could provide additional knowledge about the brain function. We can easily extend the existing connectivity methods to capture temporal fluctuations in FC, for example calculating correlation measures over sliding time-windows gives a time-series of FC (often referred to as "dynamic" or "time-varying" FC).

Characterization of time-varying FC in the brain is important not only to gain a better understanding of brain functions (Zalesky *et al.*, 2014), but also to classify clinical populations (Rashid *et al.*, 2016). In detail, time-varying measures of FC have been shown to provide important additional information regarding functional organization of the brain. For example, Zalesky and his colleagues computed window-based correlation metric to explain the dynamics of modular organization by investigating how the integration and segregation of different RSNs change by time. They found that the most dynamic connections are inter-modular, linking regions from separable systems, whereas regions composing the same module have a predominantly static nature. Their findings suggest that brain dynamics gives rise to a balance between optimizing information processing and minimizing metabolic expenditure (Zalesky *et al.*, 2014). Additionally, a previous study on classification of healthy, schizophrenia and bipolar patients suggest that dynamic FC significantly outperforms the static FC in terms of classification accuracy (Rashid *et al.*, 2016). However, sliding-window based approaches have necessary restrictions on the length of the temporal window, which in turn limits the temporal resolution of the resultant FC (Lurie *et al.*, 2018).

On the contrary, instantaneous phase synchronization offers single time-point resolution, enabling us to assess the time-varying FC with the highest temporal resolution. In this context, the synchronization is captured based on the relation between the phases of interacting regions, regardless of their amplitudes, hence it is not affected by inter subject amplitude variability. Unlike correlation and coherence, phase synchronization has the advantage of not requiring the stationarity, which is not an appropriate prerequisite in practice

(Sakkalis and Zervakis, 2009). Additionally, being a nonlinear measure of FC, makes it an appropriate choice for identification of complex dynamic processes in the brain (Glerean *et al.*, 2012; Pereda *et al.*, 2005). We note that the phases of two coupled nonlinear oscillators may synchronize, even if their amplitudes remain uncorrelated (Pikovsky *et al.*, 2002). Due to its several advantages, it has gained considerable attention in the recent literature (Omidvarnia *et al.*, 2016; Pedersen *et al.*, 2017; Ponce-Alvarez *et al.*, 2015). The instantaneous phase synchronization for each pair of regions is defined as the cosine similarity of instantaneous phases obtained from associated regions' signals. Hence, the Hilbert transformation is applied to the regional BOLD signals to derive the analytic representation of the real-valued BOLD signals and subsequently estimating the instantaneous phase of the analytic signal as the inverse tangent of the quotient formed by dividing the imaginary part by the real part of the BOLD signal.

### 2.3.3 Data-driven Functional Connectivity Analysis

*"All data has its beauty, but not everyone sees it."*

*— Damian Mingle*

So far, we have discussed the simplest FC analysis approach, namely the seed-based connectivity analysis, which involves computing pairwise interactions of a predefined voxel or ROI with the rest of brain voxels (Biswal *et al.*, 1995; Fox *et al.*, 2005; Fransson *et al.*, 2011; Nyberg *et al.*, 2016). This method can be biased by arbitrary selection of the seed region. Additionally, it only detects networks which include that particular seed region, which makes it an inappropriate method for exploratory analysis. However, data-driven methods like clustering analysis (Fadili *et al.*, 2000) and different blind source separation techniques, like Principal Components Analysis (PCA) and Independent Component Cnalysis (ICA) are capable to go beyond pairwise interactions. Among the data-driven techniques, ICA has demonstrated considerable promise for the exploratory analysis of fMRI data (Calhoun and Adali, 2006).

ICA is a multivariate data-driven technique that applies higher-order statistics to estimate maximally independent components (Calhoun *et al.*, 2001a; McKeown and Sejnowski, 1998). ICA is a technique that attempts to recover unknown source signals underlying sets of observations based on information theory. In this method, the observed multivariate data variables are assumed as linear mixtures of some hidden variables which are maximally independent of each other and are referred to as independent components/sources. ICA was a proposed approach to solve one of the most traditional blind source separation problems, the cocktail party problem, which refers to the problem of deciphering the underlying source signals (voices of different speakers) from the mixed signals recorded by several microphones in the room (Calhoun and Adali, 2006).

Compared with alternative FC methods, ICA has several advantages, such as being data-driven, independent of an a-priori temporal model (which makes it an appropriate choice for resting-state condition), and less sensitive to confounding factors such as motion. It has,

therefore, been increasingly used in resting-state research. The assumption of independence among sources can be made in either space or time, yielding two varieties of ICA which are used to discover either spatially or temporally independent components. However, spatial ICA has been the most dominant technique in the functional imaging literature due to several reasons including larger spatial dimension compared to the temporal dimension (Calhoun and Adali, 2006; Calhoun *et al.*, 2001a; McKeown and Sejnowski, 1998). Spatial ICA decomposes the fMRI data into a set of maximally spatially independent maps and their respective time-courses (Figure 2). Regions with significant contribution in each component are temporally coherent with each other. We note that statistical independence in space does not mean the same as non-overlapping components, since a given voxel may have contributions from different components.

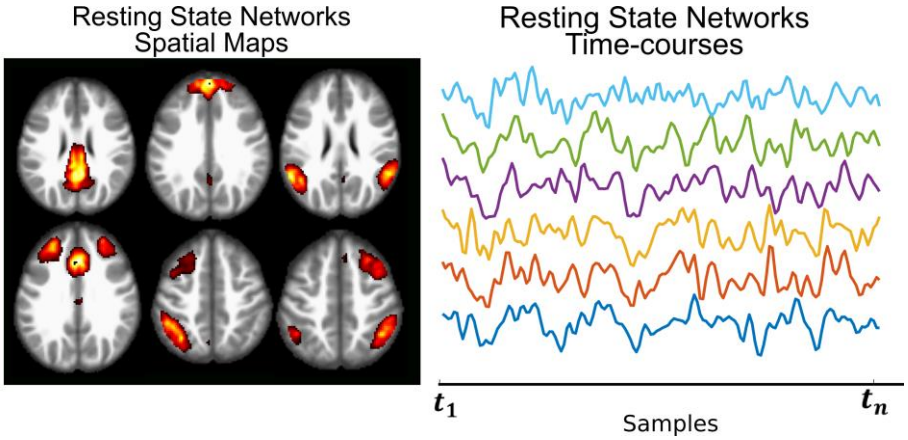


*Figure 2. Example resting-state networks and their respective time-courses, derived by applying group ICA to the resting-state fMRI data. Spatial maps in the first row are respectively associated with posterior DMN, anterior DMN and posterolateral parietal DMN centered at the temporoparietal junction. Left and right frontoparietal control networks, and the cingulo-opercular network are respectively illustrated in the second row.*

Making group inferences using ICA has flourished over the last decade and currently plays a key role in the study of brain networks (Allen *et al.*, 2011; Calhoun *et al.*, 2001b). ICA has shown to be a powerful method in identification of different types of signals of interest such as task- and function-related signals, as well as signals of non-interest including physiology- and motion-related signals (Calhoun and Adali, 2006; Du *et al.*, 2016; Glasser *et al.*, 2017; Salimi-Khorshidi *et al.*, 2014; Smith *et al.*, 2013). Figure 1 in Paper I and Paper III, are examples of resting-state networks identified by ICA.

# 3 CHAPTER 3: RESTING-STATE FUNCTIONAL CONNECTIVITY AS A BIOMARKER

*"There is therefore nothing surprising in considering the functional mental disorders as fundamentally diseases of memory, of the circulating information kept by the brain in the active state, and of the long-time permeability of synapses. Even the grosser disorders such as paresis may produce a large part of their effects not so much by the destruction of tissue which they involve and the alteration of synaptic thresholds as by the secondary disturbances of traffic — the overload of what remains of the nervous system and the re-routing of messages — which must follow such primary injuries."*

**—** *Norbert Wiener*

There is evidence that diverse measures related to FC patterns of RSNs are sensitive to psychiatric disorders (Fornito and Bullmore, 2010) and other conditions, such as Alzheimer's disease (Greicius *et al.*, 2004), Parkinson's disease (Helmich *et al.*, 2010) and stroke (Park *et al.*, 2011). In addition, age is a significant determinant of inter-individual variability in intra- and inter-network FC patterns (Andrews-Hanna et al., 2007; Geerligs et al., 2015a), and findings regarding age-related alterations in FC of RSNs have attracted considerable attention (Grady, 2012). Therefore, measures of the brain's FC may serve as a useful tool to diagnose and predict the course of disease (Zhang and Raichle, 2010), and useful in developing individualized therapies.

## 3.1 RESTING-STATE FUNCTIONAL CONNECTIVITY AND AGING

Central cognitive abilities, such as working memory and episodic memory, are highly age-sensitive according to both cross-sectional and longitudinal studies (Park *et al.*, 1996; Rönnlund *et al.*, 2005). The incidence of cognitive impairment and dementia increases exponentially with advancing age (Fratiglioni *et al.*, 2000). Such impairments come with major individual and societal costs. Hence, it is important to better understand the brain basis of cognitive decline in aging.

Developments in neuroimaging techniques have provided opportunities to investigate the aging brain in vivo (Grady, 2008). Age-related intra- and inter-individual cognitive differences have been associated with differences in various fMRI measures. Age-related FC changes have been found to be topographically heterogeneous, similar to the non-uniform profile of cognitive decline associated with normal aging. Thus, age-related cognitive impairment may, at least in part, result from disruption of RSN FC.

Age-related alterations in RSN FC could reflect a multitude of factors, including changes in structural connectivity, GM volume, and WM structure. For example, GM volume loss in a specific region may cause contamination of voxels with CSF, which affects FC due to decreased signal-to-noise ratio (Bodurka *et al.*, 2005). In addition, there is evidence that resting-state FC reflects the underlying architecture of anatomical connectivity (Damoiseaux and Greicius, 2009; Greicius *et al.*, 2009). Anatomical connectivity, as measured, for

example, by diffusion-tensor imaging, shows pronounced age-related decline according to both cross-sectional (Salami *et al.*, 2012) and longitudinal (Barrick *et al.*, 2010) studies. These alterations tend to accelerate with advancing adult age (Burzynska *et al.*, 2010). Thus, it is reasonable to assume that the loss of structural WM connectivity in aging may lead to aberrant FC, and in turn cognitive decline. Notably, there is body of evidence supporting the view that an impaired structural connectome may cause disrupted FC, contributing to neurodegenerative diseases (for example, see (Griffa *et al.*, 2013)).

There is growing consensus regarding age-related decline in FC within the DMN (Andrews-Hanna *et al.*, 2007; Damoiseaux, 2017; Ferreira and Busatto, 2013; Spreng *et al.*, 2016), as well as in failure to deactivate DMN regions during demanding tasks (Andrews-Hanna *et al.*, 2007; Damoiseaux, 2017; Ferreira and Busatto, 2013; Ng *et al.*, 2016; Spreng *et al.*, 2016). In addition, studies have found age-related alterations in between-network connectivity of brain circuits (e.g., connectivity between the DMN and the executive network) (Chan et al., 2014; Geerligs et al., 2015a; Ng et al., 2016). These changes may result in less modular or segregated networks in aging (Chan et al., 2014; Geerligs et al., 2015a; Ng et al., 2016). Note that these studies are primarily based on cross-sectional data, and the biological mechanisms underlying connectivity disruptions in the DMN are not yet clearly understood. There are observed associations between decline in DMN FC and loss of GM and WM integrity in the DMN (Andrews-Hanna *et al.*, 2007; He *et al.*, 2009). Based on previous reports linking DMN connectivity and self-referential cognitive processes (Buckner and Carroll, 2007), it is reasonable to assume that a lower level of DMN within-network connectivity partly accounts for age-related cognitive impairments. Moreover, longitudinal studies of age-related changes in different DMN subsystems are scarce. This is an important omission, as the actual rate of age-related changes as well as the onset of disruption in DMN FC can only be accurately estimated using longitudinal data.

### 3.1.1 Theories of Aging

Theories are parsimonious explanations of why different concepts are interconnected. However, no single theory can explain all aspects of a phenomenon perfectly. Therefore, theories are not mutually exclusive; they might partly overlap and even complement each other. Here, I will briefly review a few of the theories that try to map age-related cognitive decline to changes in the brain. These theories are “cognitive reserve”, “compensation”, “brain maintenance”, and “brain plasticity”.

The concept of “cognitive reserve” was proposed to address the disconnection between level of brain damage and clinical outcomes. Although many people are sensitive to brain damage, some people can tolerate more damage than others and still maintain a high level of function. Cognitive reserve-enhancing factors include various aspects of life, such as educational and occupational attainment, physical exercise, and leisure activities particularly in late life. These factors allow some individuals to cope better than others with progressing accumulation of damage (Stern, 2009). Thus, we do not observe a linear relationship between brain damage and cognitive decline. This account is used in epidemiology to explain reduced

risk of dementia and slower cognitive decline for individuals with more exposure to educational, occupational, physical, and leisure activities (Fratiglioni *et al.*, 2004; Stern, 2009). A possible neurobiological mechanism is "efficiency" and "flexibility" of brain networks (for example extracted from fMRI data). This notion may be studied by applying graph theory-based analysis with a prediction that individuals with preserved functional architectures (e.g. preserved modularity) in older age are those with greater reserve-enhancing factors.

Another perspective in this field is called "compensation theory". This theory postulates that when brain structures and consequently functional networks are interrupted by malfunction somewhere in the brain, other brain regions and networks will cope with the dysfunction, because of synergy among them (Bäckman and Dixon, 1992). This may be manifested in the form of greater activity or stronger FC somewhere in the brain, in response to an emergent fault (Cabeza and Dennis, 2013; Grady *et al.*, 1994). On the other hand, the "brain maintenance theory" is based on the notion that elderly individuals who preserve their cognitive performance levels may have relatively intact brains (Nyberg *et al.*, 2012).

Adherents of both "compensation theory" and "brain maintenance theory" claim that there is an association between changes in brain properties (for example at the functional-connectivity level) and changes in cognitive performance. By examining the direction of association between FC changes and cognitive decline, one might find any evidence supporting either compensation or maintenance theories, or even a combination of both. For example, if we hypothesize that segregation/modularity of brain networks declines with advanced age, then we might face two different scenarios, in which accounts compete against each other:

I. The level of decline in segregation is positively correlated with cognitive performance decline, which would support the brain maintenance view;

II. The level of decline in segregation is negatively correlated with decline in cognitive performance, which would support the brain compensation view.

Finally, the "brain plasticity theory", assumes that our brain shows lifelong capacity for adaptive structural and functional changes in exposure to environmental demands and experience. These changes are bidirectional such that brain function can get strengthened or weakened, depending on the conditions. In normal aging, accumulative effects of physical, behavioral, and environmental changes may cause brain plasticity that affects brain function. The key reasons behind functional decline are structural brain downturn (e.g., noisy processing and inadequate neuromodulatory control) and behavioral and environmental changes (e.g., less scheduled brain activity). The interplay among these factors results in a self-reinforcing downward spiral of degrading brain function in advanced age (Mahncke *et al.*, 2006).

The “brain maintenance” and “compensation” theories may be useful in explaining the link between age-related changes in FC patterns and decline in episodic memory, as investigated in the first study in this thesis.

## 3.2 RESTING-STATE FUNCTIONAL CONNECTIVITY AND ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

ADHD is characterized by high distractibility and impaired executive functions such as working memory and cognitive control. A large number of neuroimaging studies have targeted structural and functional brain activity changes related to the impairment of executive functioning and attentional processes in the ADHD cohorts (Bush, 2010; De La Fuente et al., 2013; Konrad and Eickhoff, 2010; Krain and Castellanos, 2006; Martínez et al., 2016). Task-based fMRI studies have noted altered brain function involving areas in the frontal, temporal and parietal lobes (Krain and Castellanos, 2006; Wilens and Spencer, 2010). However, no consensus agreement has yet been reached (Hoogman *et al.*, 2017; Konrad and Eickhoff, 2010; Samea *et al.*, 2019). With regard to static (i.e. by computing the temporal mean of correlation) resting-state fMRI, previous studies have reported significant ADHD-related dysfunctions for both cognitive control networks and the DMN. Failures in regulating the dynamics of activity and interactions between these large-scale networks have been hypothesized as the underlying functional mechanisms for impaired cognitive control. Cognitive control regions separate into frontoparietal control network (FPN) and cingulo-opercular network (CON) (Dosenbach *et al.*, 2008; Marek and Dosenbach, 2018). The FPN is optimized for rapid adaptive control, whereas the CON is known for stable task-set maintenance (Dosenbach *et al.*, 2008) and sustained attention/tonic alertness in general (Sadaghiani and D’Esposito, 2015; Sadaghiani *et al.*, 2010). Existence of such parallel control architecture gives rise to a flexible but highly stable behavior, increasing the resilience of top-down control to perturbations (Dosenbach *et al.*, 2008).

The FPN (or executive control network), seems to support phasic aspects of attentional control such as initiation and adjustment of control signals as well as decision-making processes. It comprises the lateraled prefrontal parietal network including bilaterally the lateral prefrontal cortex, dorsal frontal cortex, inferior parietal lobule and precuneus (Corbetta *et al.*, 2002; Dosenbach *et al.*, 2008; Sadaghiani and D’Esposito, 2015; Vincent *et al.*, 2008). The CON (also referred as salience network) is the other cognitive control network, anchored in the anterior insula and dorsal anterior cingulate cortex, which was primarily known as being involved in integrating sensory data with autonomic, visceral and somatic markers, in order to identify the biologically and cognitively relevant stimuli (salient events), particularly to facilitate attentional reorienting and access to memory resources in high-level cognitive control and attentional processes (Menon and Uddin, 2010; Sevinc *et al.*, 2017; Sridharan *et al.*, 2008). Additionally, activity in the cingulo-opercular regions regulates the activity and interactions of the DMN and FPNs (Di and Biswal, 2014; Menon and Uddin, 2010; Sevinc *et al.*, 2017). Therefore, this network has a key role in the hierarchical initiation of cognitive control signals, particularly in relation to the dynamics of switching between other large-scale

networks (Di and Biswal, 2014; Menon and Uddin, 2010; Sevinc *et al.*, 2017). In a different line of research, where aforementioned regions are more often referred as the CON (rather than salience), strong evidence suggests a quite different functional role for this network. In this view, the fundamental function of CON is set-maintenance activity (Dosenbach *et al.*, 2008; Sadaghiani and D'Esposito, 2015) and even more broadly, it is suggested to underlie maintained tonic alertness/sustained attention (Sadaghiani and D'Esposito, 2015; Sadaghiani *et al.*, 2010). Indeed, a previous fMRI-EEG study proposed that the CON serves maintaining tonic alertness by employing cortical alpha oscillations to suppress task-irrelevant information causing distraction and maintain cognitive faculties accessible for current processing demands (Sadaghiani *et al.*, 2010).

In relation to ADHD, unsuccessful suppression of the default mode network (DMN) and failure in regulation of signaling between the DMN and FPNs have been suggested as the key underlying functional mechanism for impaired cognitive control. Additionally, a large body of research indicated the presence of pronounced fluctuations in the strength of functional connections over time (for example see, (Hutchison *et al.*, 2013)), particularly for the inter-network connections between the DMN and FPNs (Zalesky *et al.*, 2014). However, the importance of the temporal dimension, both in terms of measurements of fMRI brain connectivity as well as the nature of ADHD symptoms, have previously not been adequately taken in account. Importantly, one of the most prominent signatures of disrupted cognitive processing in ADHD subjects is the pervasive temporal lapses of attention, the reoccurring signs of impulsivity and interferences during tasks (Sonuga-Barke and Castellanos, 2007). Clearly, the temporal fluctuations of cognitive impairment as typically observed in ADHD do not easily lend themselves to be fully described using conventional linear modeling of task-related BOLD responses or to static network measures of functional brain connectivity.

In the context of ADHD brain connectivity, of particular interest are the previously observed temporal fluctuations in the strength of connectivity between the DMN and the cognitive control networks (FPN and CON). It has been suggested that the interaction between these networks that efficiently balance network segregation and integration across various neural dynamical scenarios over time may play a pivotal role in the manifestation of the aforementioned fluctuations in cognitive performance in ADHD (Broyd *et al.*, 2009). Moreover, it has been shown that individuals with ADHD, compared to healthy individuals, have a higher variability in their resting-state BOLD signals (Mowinckel *et al.*, 2017; Nomi *et al.*, 2018).

With that said, it is reasonable to think that a connectivity analysis approach that is capable of providing a fine-grained account of the dynamic nature of interactions between different networks is required to a better characterization of putative abnormal brain network configurations linked to ADHD.

# 4 CHAPTER 4: DYNAMICAL SYSTEMS THEORY

*"Chaos: When the present determines the future, but the approximate present does not approximately determine the future."*

*— Edward Lorenz*

Dynamical systems theory is a mathematical framework used to describe the behavior of dynamical systems, that is, systems that evolve with respect to time. Accordingly, the dynamical system may be defined as a rule (or model) for time evolution of the state of a system, providing a prediction of the consequent(s) to a given current state. Time can be either thought of as a continuous or a discrete integer-valued variable. If there is a theoretically unique consequent to an initial state value, the evolution rule and the related system are said to be deterministic. Otherwise, if there is a probability distribution of possible consequents, it is called a stochastic or random system (Ott, 2002; Strogatz, 2015).

The dynamical systems theory provides a level of convergence which enables the unification and linking of physical characteristics of biological systems and multiple behavioral phenomena. Indeed, various biophysical changes may bring on the same dynamical phenomena (for example oscillations, attractors and etc.), whereas similar changes in dynamical phenomena may cause unlike behavioral symptoms. Putting the focus on dynamics, with such a property, could have implications for a better diagnosis and prognosis, as well as designing optimal and robust goal-directed therapies for the treatment of psychiatric disorders (Durstewitz *et al.*, 2018).

## 4.1 NONLINEAR DYNAMICS — MODEL-BASED ANALYSIS

*"The whole is greater than the sum of its parts."*

*— Aristotle*

The analysis techniques for the linear systems are largely based on superposition principle. Indeed, linear systems can be broken down into parts that can be solved independently and finally the individual solutions will be combined to get a solution for the whole-system. However, the analysis of nonlinear dynamic systems is encountered with solving one complex problem that cannot be chopped into smaller parts. Poincare in the late 1800s introduced a new geometric approach suggesting a qualitative rather than quantitative perspective, which can be considered as the biggest step forward in the analysis of nonlinear dynamic systems. His geometric reasoning was further developed during the late 19th century, and resulted in the concept of state space (or phase space) which is a useful construction to handle dynamical systems and perform qualitative geometrical analysis (Izhikevich, 2010; Ott, 2002; Strogatz, 2015).

The state space of a dynamic system is an abstract space with a coordinate system which is spanned by all system variables, which are required to describe the state of that particular system. Every potential system state can be represented with a unique point in the state space.

For any particular initial condition, the time evolution of a state (i.e., the time evolution of all system variables) can be plotted as a curve in the state space which is referred to as a trajectory. Trajectories provide information about the behavior of dynamical systems. Therefore, we can draw the state space trajectories and extract information about the system behavior (solutions of the differential equations) qualitatively without analytically solving the equations driving the system's dynamics (Strogatz, 2015).

In a dynamical system, fixed points (equilibrium points) of the system are all points where there is no flow in the system (i.e., the derivative of system's state variable is equal to zero). Consider a one-dimensional dynamical system, in which temporal evolution of the state variable $x(\mathrm{t})$, that is its first derivative with respect to time ($\dot{x} = \frac{dx}{dt}$), is described by a scalar function ($\dot{x} = f(x)$). The fixed points of the system are the values of the state variable (symbolized by $x^*$),where $f(x^*) = 0$. If the initial value of the state of the system ($\mathrm{x}_0$) is set exactly to a fixed point ($x^*$), then the state variable will rest there, otherwise if the initial state ($\mathrm{x}_0$) is set close to a fixed point ($x^*$), the state variable may either converge to that fixed point or diverge from it (denoted by the vector ($\mathrm{f}(\mathrm{x}_0)$) in state space). In a nutshell, fixed points represent steady state solutions which do not change by time. Local stability of fixed points in a one-dimensional system can be easily determined by comparing the sign of the function that determines the time evolution of that system ($f$), before and after any fixed point. If the sign of $\mathrm{f}(x^*)$ changes from negative to positive, in other words the derivative of function $f$ with respect to $x$ at the fixed point is positive ($\frac{\partial f}{\partial x}\Big|_{x=x^*} > 0$), therefore the fixed point is unstable. Otherwise, if the sign of $\mathrm{f}(x^*)$ changes from positive to negative, in other words the derivative of function $f$ with respect to $x$ at the fixed point is negative ($\frac{\partial f}{\partial x}\Big|_{x=x^*} < 0$), the fixed point is stable. A stable fixed point is said to be an attractor, since it attracts all the solutions in its neighborhood. A stable fixed point is the only type of attractor that a one dimensional continuous dynamical system can have, however other types of attractors can exist in systems with higher dimensionality.

Consider a two-dimensional dynamical system (or a planar system), in which temporal evolution of the 2-dimensional state variable, as defined by variables $\mathrm{x}(\mathrm{t})$ and $\mathrm{y}(\mathrm{t})$, is described by the functions f and g. In the general framework of coupled ordinary differential equations, it can be written as below:

$$\begin{cases} \dot{x} = f(x,y) \\ \dot{y} = g(x,y) \end{cases} \xrightarrow{\dot{x}=0 \; and \; \dot{y}=0} (x^*, y^*) \checkmark$$

The equilibrium points of this system are derived by simultaneously solving $\dot{\mathrm{x}} = 0$ and $\dot{\mathrm{y}} = 0$. If the initial value of the state of the system $(\mathrm{x}_0, \mathrm{y}_0)$ is set exactly to the fixed point, then the state variables will not change by time, otherwise if the initial state is close to the fixed point the state variables may either converge to the fixed point or diverge from that (denoted by the vector $(\mathrm{f}(\mathrm{x}_0, \mathrm{y}_0), \mathrm{g}(\mathrm{x}_0, \mathrm{y}_0))$ in state space). Local stability of a fixed point in higher dimensional systems requires a further evaluation of the sign of the real part of eigenvalues

obtained from the Jacobian matrix at the fixed points. Generally, fixed points can be categorized by evaluating the eigenvalues of the Jacobian matrix at these points, which subsequently helps in determining the qualitative behavior of the system in the neighborhood of fixed points. The Jacobian of a system is the matrix of all its first-order partial derivatives regarding its state variables, defined for a fixed point $(x^*, y^*)$:

$$J = \begin{bmatrix} \frac{\partial f}{\partial x} & \frac{\partial g}{\partial x} \\ \frac{\partial f}{\partial y} & \frac{\partial g}{\partial y} \end{bmatrix}_{\substack{x=x^* \\ y=y^*}} \xrightarrow{|\lambda I - J| = 0} \lambda_{1,2} = \alpha \pm j\beta$$

We note that a nonlinear system can have many fixed points and accordingly the Jacobian matrices are defined for each fixed point, separately. The eigenvalues of the matrix $J$ are values of $\boldsymbol{\lambda}$ for which the determinant of the matrix $\lambda I - J$ is zero, where $I$ is the identity matrix. If the eigenvalues of the fixed point ($\lambda_1$and $\lambda_2$) are real numbers (i.e., $\beta = 0$) and of the same sign, the fixed point is called a Node (the first letter is capitalized to highlight its difference from the term node as it will be later used in the definition of networks). Positive eigenvalue implies instability, whereas negative eigenvalue implies stability of the Node (Figure 3, first row).

Having eigenvalues which are complex conjugate numbers is an indication of spiral behavior in the state space and the respective fixed points are referred to as a "focus". In this case, the stability of the fixed point can be determined based on the sign of the real part of the eigenvalue. In other words, if $\alpha < 0$, then the focus is a stable equilibrium with solutions spiraling into that (spiral sink). However, if $\alpha > 0$, then the focus is unstable (spiral source) with solutions spiraling out from that (Figure 3, second row). The frequency of rotation of trajectories around this type of fixed point can be determined from the imaginary part of the eigenvalues ($\beta$) (Hilborn, 2000; Kuramoto, 1984; Strogatz, 2015).

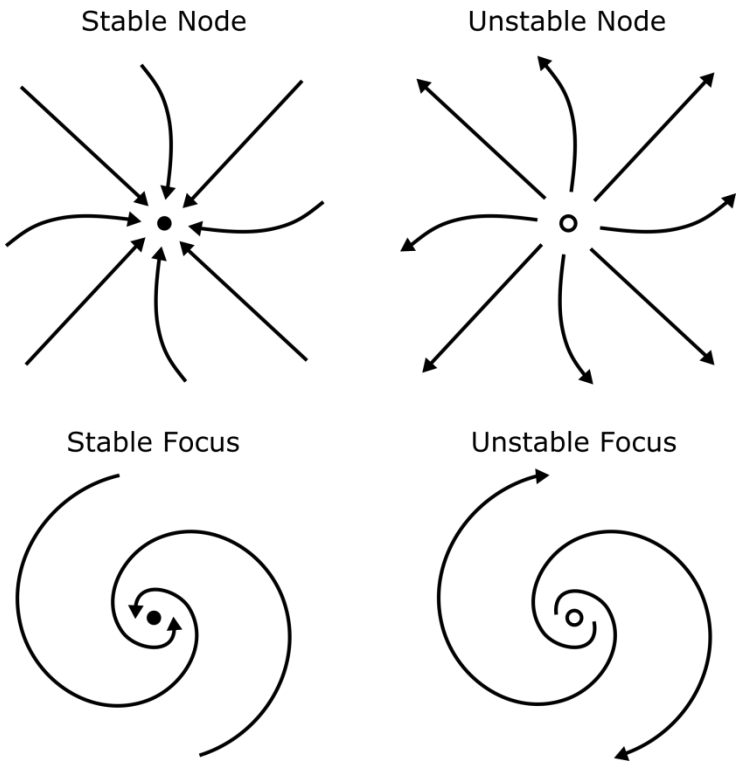


*Figure 3. When the eigenvalues of a fixed point have the same sign, the fixed point is called a Node. If the eigenvalues are complex-conjugate, respective fixed point is called a focus.*

As mentioned earlier, a stable fixed point is not the only possible attractor for a two dimensional dynamical system. Indeed, other types of attractors such as limit cycles can exist in systems with two or higher dimensionality. A limit cycle is an isolated closed trajectory in the state space with the neighboring trajectories spiraling toward or away from that. A limit cycle in the state space corresponds to a special type of solution for a system, representing the periodic behavior of that dynamical system. The limit cycle is stable if all the trajectories in its neighborhood approach it. Solutions that reside inside of the closed orbit will spiral out towards the orbit, while solutions outside of the orbit will spiral inward. If the initial value of the state variable is on a limit cycle, then the state space solution remains on that periodic trajectory forever, exhibiting a periodic behavior for the system. In the planar systems, there is always at least one fixed point inside any limit cycle (Izhikevich, 2010; Strogatz, 2015). It is intuitively expected that inside a stable limit cycle, there must be an unstable equilibrium point or an unstable limit cycle, since neighboring trajectories spiral toward the stable limit cycle.

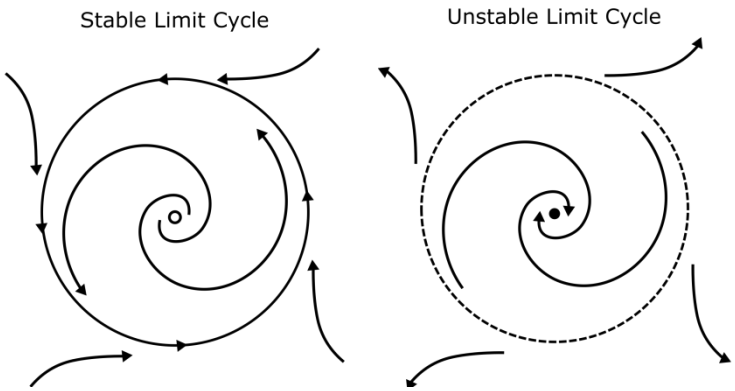


*Figure 4. Examples of stable and unstable limit cycles. Left panel shows an unstable focus inside a stable limit cycle, and the right panel shows the opposite.*

Stable limit cycles model dynamic systems showing self-sustained oscillations (i.e., the type of oscillating behavior which persists even in the absence of external periodic forcing or facing with slight perturbations). Relatively, a dynamical system displaying a stable limit cycle in the state space is usually known as an oscillator. Oscillator systems are abundant in nature. They are often described as systems that produce a continuous, repeated, alternating output (so called oscillations) without any input. In other words, oscillation can simply denote something moving back and forth. Familiar examples of oscillation include beating of the human heart, a person's sleep-wake patterns and a swinging pendulum. Neural oscillations are rhythmic or repetitive neural activity patterns driven either by individual neurons (e.g., oscillations in membrane potential) or via interactions among neurons in neural ensembles (e.g., macroscopic neural oscillations observed during electroencephalography). Different types of oscillators in virtually every area of science share this amazing feature that they can be defined only by a single phase variable, rotating on a circle. Oscillators with weak interactions with each other can adjust their oscillating rhythms (synchronize) and display collective behavior that is not intrinsic to any individual oscillator. The word “synchronous”, which means “occurring in the same time”, and related terms like “synchronization” refer to a variety of seemingly different phenomena that can be understood within a common framework based on dynamical systems theory (Hoppensteadt and Izhikevich, 1997; Pikovsky *et al.*, 2003). Using phase models to understand the collective dynamics of many coupled oscillators will be described later in the computational modeling of brain network.

Systems with nonlinear dynamics, even the ones with only one dimension, can show a peculiar dynamical behavior, namely bifurcation. Bifurcation refers to an abrupt qualitative change in the behavior of a nonlinear system, caused by applying a slight change to a control parameter of the system. Ubiquitous patterns of bifurcations have been identified, resulting in their categorization to different bifurcation types. For example, one of the most fundamental bifurcations is the Hopf bifurcation which occurs when the stability of the equilibrium of a system switches, and it gives birth to a limit cycle. If the resultant limit cycle is stable, the

bifurcation is called a supercritical Hopf bifurcation otherwise it is called a subcritical Hopf bifurcation when the limit cycle is unstable (Hilborn, 2000; Kuramoto, 1984; Strogatz, 2018).

## 4.2 NONLINEAR DYNAMICS — MODEL-FREE ANALYSIS

*"Certain systems will, after a sufficiently long but finite time, return to a state very close to (for continuous state systems), or exactly the same as (for discrete state systems), their initial state."*

*— Poincaré recurrence theorem*

We note that the dynamical system theory relies on the concept of state space which can be derived from the underlying system's differential equations or theoretically by having time-varying measurements of all the state variables. Typically, the system's differential equations are not known, and on the other hand constructing the state space is commonly confronted with a time-varying measurement of only one observable system variable, since not all system variables are measurable. One suggested solution is to apply the time-delay reconstruction technique, which is a frequently used method for state space reconstruction (Takens, 1981), based on the time delayed values of the observed system variable. This technique approximates an attractor in higher dimension space, assuming that variables which were not measurable are probably somehow depending on the sequence of numbers generated from observations of the system, but lagged at some time scale (time delay). Time delay ($\tau$) and embedding dimension ($m$) are two parameters regarding this technique that need to be estimated. Embedding dimension is the number of degrees of freedom which is sufficient to describe key properties of the state space according to the delay embedding theorem (Takens, 1981). Using such a model-free approach for studying the dynamical systems properties has several practical advantages, by obviating the need for developing an accurate mathematical model of the system.

In practice, when given a scalar time series of whatever origin, embedding parameters are not known a priori. The optimal embedding parameters (the embedding dimension $m$ and the time delay $\tau$), can be estimated utilizing the amount of false nearest neighbor (Kennel *et al.*, 1992) and mutual information algorithms, respectively. It is shown that a good candidate for an appropriate time delay $\tau$ is when the statistical dependence between the components of the embedding vector approaches zero. A well-established strategy is to compute the mutual information between the time-series and its delayed versions, for different values of delay, and subsequently select the appropriate delay as the one at which the time delayed mutual information exhibits an obvious minimum. Afterwards in order to estimate the optimal embedding dimension $m$ according to the concept of false nearest neighbors algorithm (Kennel *et al.*, 1992), one can examine how the proximity relations between state-vectors change as a function of successive increase in the embedding dimension. Indeed, there will be many false neighbors for the too low values of embedding dimension, whereas by choosing an appropriate embedding dimension (or higher), the neighbors are real. Hence, we can

determine a reasonable embedding dimension $m$ by examining how the number of neighbors changes as a function of dimension (Kennel *et al.*, 1992).

State space reconstruction provides astonishing applications for different problems in the analysis of real data. In some circumstances, it can help us to get a general expression of the whole dynamics and the behavior of a system, for example to distinguish between periodic and chaotic behaviors. Additionally, it can be utilized for an approximate estimation of the key properties of dynamical systems, like the Lyapunov exponent which characterizes the average exponential separation rate of initially nearby state space trajectories. A positive value of Lyapunov exponent is the characteristic of a chaotic system (Josiński *et al.*, 2015).

A fundamental property of deterministic dynamical systems is that after some time the trajectory returns to an approximately close location it has visited previously (Ott, 2002; Poincaré, 1890). Therefore, by evaluating statistical similarity between different segments of a time-series, we can identify the times at which the trajectory of the system visits approximately the same area in the state space (Marwan *et al.*, 2007). States which are in an ε-neighborhood of each other characterize recurrence points which can be exploited to investigate a high dimensional state space trajectory via a two-dimensional recurrence plot. A recurrence plot is a binary graph in which recurrent and non-recurrent pairs of state vectors are respectively illustrated as black and white points (Eckmann *et al.*, 1987). Figure 5 represents an illustrative example of a toy signal, applying the mutual information and nearest neighbor tests for the estimation of its parameters, reconstructed state space trajectory and finally its respective recurrence plot.

Recurrence plots exhibit characteristic large-scale patterns of recurrences classified as homogenous, periodic, drift or disrupted, which are associated with particular dynamics of the system (Marwan *et al.*, 2007). Due to the characteristic behavior of the state space trajectory recurrence points may stay as individual dots or form other small-scale structures, characterized as diagonal lines, vertical/horizontal lines or a combination of both. If the values of state strongly fluctuate, they can be revisited only for a considerably short duration, appearing as single dots. When a segment of the trajectory in the state space runs parallel to another segment, so that the trajectories evolve through the same ε-tube for some time, we observe a diagonal line in the recurrence plot. However, a vertical (horizontal) line structure characterizes a state that is trapped for some time because the state is not changing or it is changing very slowly (Marwan *et al.*, 2007).

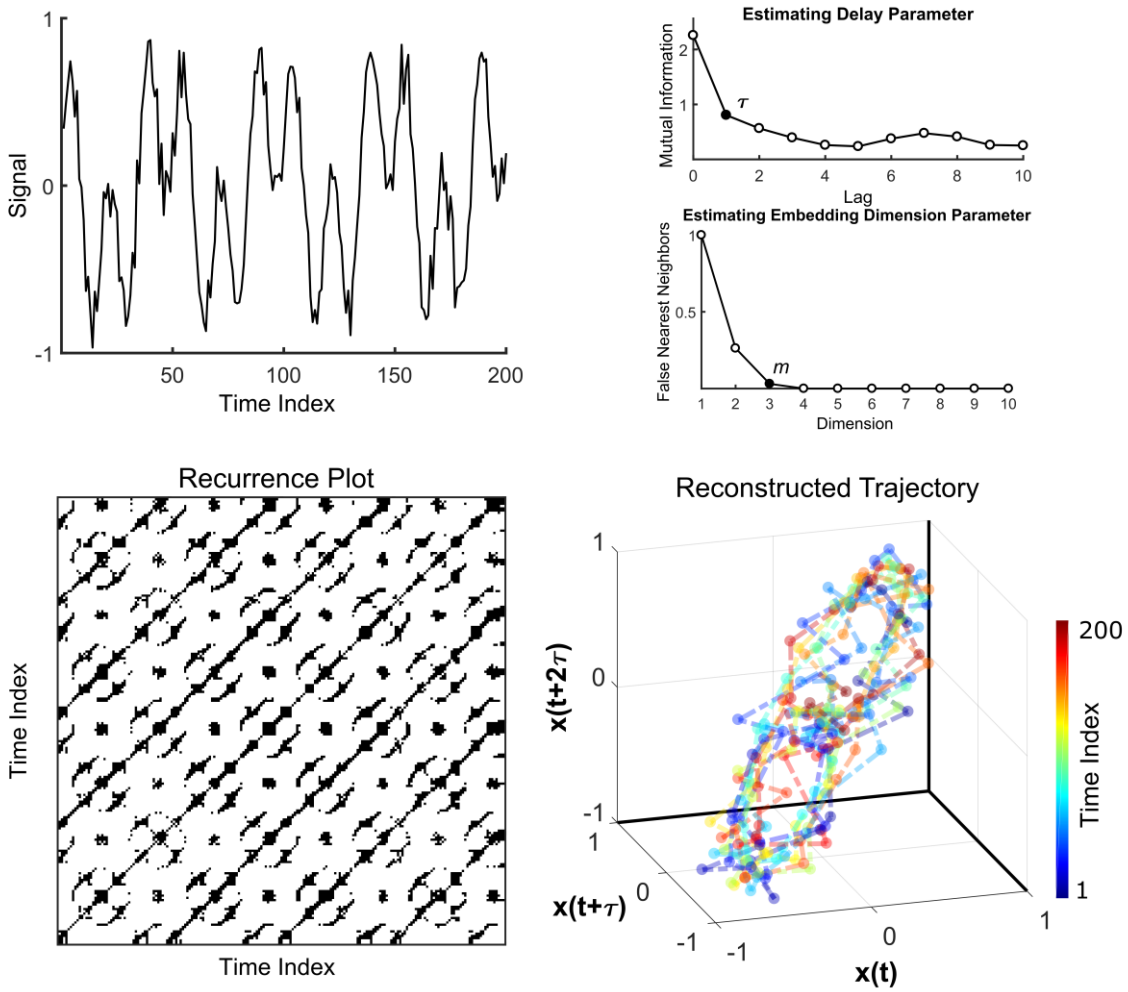


*Figure 5. For the illustrated toy signal, the optimal values for the time delay $\tau$ and embedding dimension $m$ were estimated as the location of the knee of curves associated with the auto mutual information and the amount of false nearest neighbors respectively. According to the appropriate parameter set ($\tau = 1$, $m = 3$), the state space trajectory is reconstructed and subsequently its respective recurrence plot is depicted (threshold was arbitrarily set to 0.4).*

In order to evaluate the recurrence plot in a quantitative approach, small-scale recurrence structures can be employed in the recurrence quantification analysis (Zbilut & Webber 1992; Marwan et al. 2002). Recurrence rate is the simplest quantifiable measure which is simply the density of recurrence points. Determinism or predictability of the system can be measured by computing the ratio of recurrence points that form diagonal lines with the minimum length to all the observed recurrence points. The average length of diagonal lines is introduced as a measure of mean prediction time. In addition, the length of maximum diagonal line can be utilized to measure the divergence speed of trajectory segments, so that the shorter diagonal lines represent the faster divergence of trajectory segments. Laminarity of the system is introduced as the ratio of recurrence points that form vertical lines to all the observed

recurrence points, comparative to the description of the determinism. Additionally, the average time interval that the system is trapped at specific states is known as trapping time (Marwan *et al.*, 2007).

Notably, a state space based recurrence plot can be treated as a network, in which the sampled state vectors are interpreted as vertices and recurrences are interpreted as edges. In other words, any pair of state vectors which are mutually close in the state space will be represented by an edge connecting them to each other. Reinterpretation of recurrence plots in the framework of network theory provides new analysis concepts for discovering hidden patterns in a time-series. Similar to any other network, graph theoretical measures (which will be explained in the next chapter) that characterize the individual vertices or individual edges, as well as global network characteristics can be utilized for the analysis of recurrence networks. For example, the nodal degree characterizes local recurrence rate of an individual state, and the average path length represents the average state space separation of states. Recurrence networks have been previously suggested as a complex network approach to nonlinear time-series analysis (Donner *et al.*, 2011; Zou *et al.*, 2018).

# 5 CHAPTER 5: NETWORK SCIENCE

*"All models are wrong, but some are useful."*

*— George Box*

Network science is an interdisciplinary field which studies the structure and function of networked systems, such as biological systems and telecommunication networks, that are composed of numerous elements interacting with each other (Sporns, 2018). We focus on graph theory as the principal mathematical scaffold behind the network science (Barabási, 2016), although a repertoire of other theories and methods from different fields (e.g., data mining and statistical inference) are employed in the network science, too.

## 5.1 GRAPH THEORY

*"Mathematics is the art of giving the same name to different things."*

*— Henri Poincaré*

Systems consisting of different interacting units are naturally represented as a graph with a set of vertices (or nodes) and their mutual interactions (i.e., edges or links), which in their simplest form can be described in the form of a 2-dimensional adjacency matrix (Sporns, 2018). The two nodes which are linked are said to be adjacent. Indeed, the two different terminologies ({network, node, link} and {graph, vertex, edge}) can be used interchangeably, although there is subtle distinction made by Barabási suggesting that the first set usually refers to real systems (e.g., brain as a network of regions linked by FCs), whereas the latter seems more appropriate for the discussions around mathematical representation of networks (Barabási, 2016).

Graph theory has attracted exponentially increasing attention in analyzing large-scale neuronal communications in the brain, as it provides the simplest approach to capture the organizational properties of brain network. The functional architecture of the brain is readily characterized as a network of interacting elements, which makes graph-theoretical frameworks ideal for comprehensive studies of brain connectivity (Bassett and Sporns, 2017; Sporns, 2018). Depending on the measurement technique, brain can be mathematically characterized as a graph with a set of vertices representing either individual neurons or entire brain regions and a set of edges representing synaptic connectivity among neurons or inter-regional FCs (Sporns, 2018). The sequence of analytic steps in creating a connectivity matrix for resting-state fMRI data is illustrated in (Figure 6, left column). As such, it is possible to estimate various key measures of the brain as a whole, its subsystems, or individual nodes (Harary, 1969; Newman *et al.*, 2011; Sporns, 2018), allowing us to characterize different aspects of this network. Brain network analyses may provide unique insights for understanding intra- and inter-individual differences as well as group differences in brain architecture (Aerts *et al.*, 2016; Simpson and Laurienti, 2016).

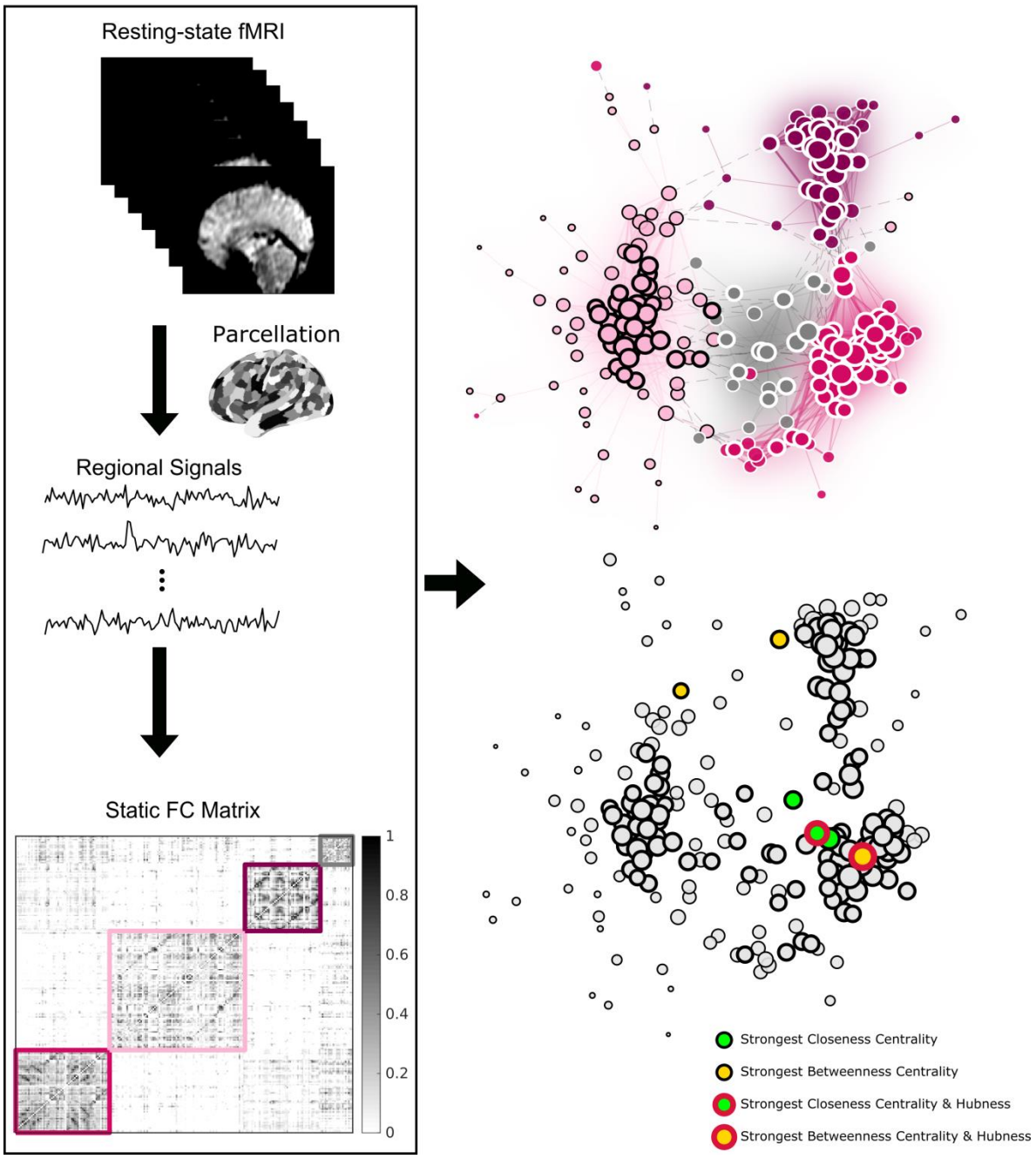


*Figure 6. Average regional BOLD signals were extracted from pre-processes fMRI data, based on an arbitrary brain parcellation. The entries of the connectivity matrix correspond to Pearson correlation coefficients (color-coded) of the BOLD signals associated with each possible pair of brain regions. The data source for creating this figure was the resting-state fMRI data from Human Connectome 500 subject release and its associated parcellation derived by performing gray matter segmentation on the T1-weighted images. We calculated the group-level static FC matrix by averaging the z-transformed subject-level connectivity matrices and illustrated the positive matrix entries. Subsequently, the optimal community structure was extracted by applying Louvain algorithm with iterative community fine-tuning. Resultant four communities are displayed in different colors. The size of nodes varies by their level of connectedness. We computed a composite hub score using average of three different unity-based normalized centrality measures (including degree, closeness centrality and*

*betweenness centrality). Relative thresholding (15%) was applied prior to extracting centrality measures. Various centrality measures might rank the network nodes in different orders.*

Brain networks can be decomposed into several subgroups of highly connected nodes, often termed as modules or communities, indicating some commonality or specialization of function (Figure 6). Each module comprises nodes, which are more densely connected to each other than to nodes from other modules (Fornito *et al.*, 2016). Typically, modular networks have "small-world" characteristics. A high clustering coefficient and a low characteristic path length are key properties of a small-world network. The clustering coefficient, which is quantified as the ratio of the count of present edges to the entire number of potential edges between the neighbors of a node captures the level to which the neighbors of that particular node are connected to each other. One can compute the clustering coefficient either at the nodal-level or across the whole network (by averaging it across all the nodes of the network). The characteristic path length is the mean of shortest paths connecting the network's nodes. A feasible contiguous sequence of edges from one node to another one is called a walk, and a path is defined as a walk in which all nodes and edges are unique. The shortest path between two nodes corresponds to the path with the smallest number of edges that connect these two nodes, and its length is called geodesic or topological distance. A network with a small characteristic path length shows strong global efficiency (Barabási, 2016; Fornito *et al.*, 2016).

In addition, there is a broad set of measures, termed as centrality measures, reflecting the importance of a node for network integration (Barabási, 2016; Fornito *et al.*, 2016; Rubinov and Sporns, 2010; Sporns *et al.*, 2007). Centrality measures are computed based on different aspects of the topological organization of a node, and are selected depending on the exact nature of the scientific question at hand (van den Heuvel and Sporns, 2013). Among centrality measures, betweenness and closeness centrality (Freeman, 1977; Sporns *et al.*, 2007) are computed based on the shortest paths in a network. Betweenness centrality of a node reflects the proportion of the shortest paths among all other nodal pairs going through that particular node. As such, a node with the highest betweenness centrality mediates most of the traffic while controlling information transfer within a network. Closeness centrality is typically computed as the inverse of the average topological distance of a particular node, to all the other network nodes, such that a node with higher closeness centrality on average has a shorter topological distance to the other nodes. There is another set of measures that quantifies the centrality of a node based on its connections (i.e. connectedness). One such measure, the so-called degree, is derived by counting the number of direct links between a given node and the rest of the network. Nodal strength, on the other hand, is the sum of weights of direct links connected to the node. Eigenvector centrality is computed by considering the overall connectivity pattern of the network and based on the concept that being connected to nodes with higher centrality is more beneficial than to nodes with lower

centrality. Therefore, a node with the high eigenvector centrality represents a highly connected node, which is connected to other highly connected nodes (Fornito *et al.*, 2016; van den Heuvel and Sporns, 2013; Zuo *et al.*, 2012).

The aforementioned measures may also be computed considering the spatial distribution of connections. For example, the participation coefficient of a node is computed based on the distribution of intra-module connections, in relation to the total connections of the node. Therefore, a higher participation coefficient indicates proportionally greater communication with nodes in other modules. There is also a within-module version of degree, known as the within-module degree z-score (Guimerà and Amaral, 2005). Different centrality measures might rank the network nodes in different orders (Zuo *et al.*, 2012). However, nodal rankings based on different centrality measures are often associated (van den Heuvel and Sporns, 2013). Therefore, it may be suggested to aggregate different standardized centrality scores and create a composite measure of hubiness for an overall classification of nodes (Rubinov and Sporns, 2010; van den Heuvel and Sporns, 2013). Identification of the hubs which are the most central nodes in a network is a controversial topic, with a large range of opinions based on different centrality measures. For example, one of the first proposals proffered has three key features (Freeman, 1978): First, it evaluates the maximum number of connections (nodal degree) compared to the rest of network nodes. Existence of highly connected network nodes is based on the fact that the distribution of connectivity is not uniform across the nodes of the brain. Second, the central node has the shortest path length (i.e., maximum closeness) to all other nodes. Third, it is located on the shortest possible topological path between all pairs of nodes. Figure 7 illustrates different nodes with the highest betweenness, closeness, degree, and eigenvector centralities.

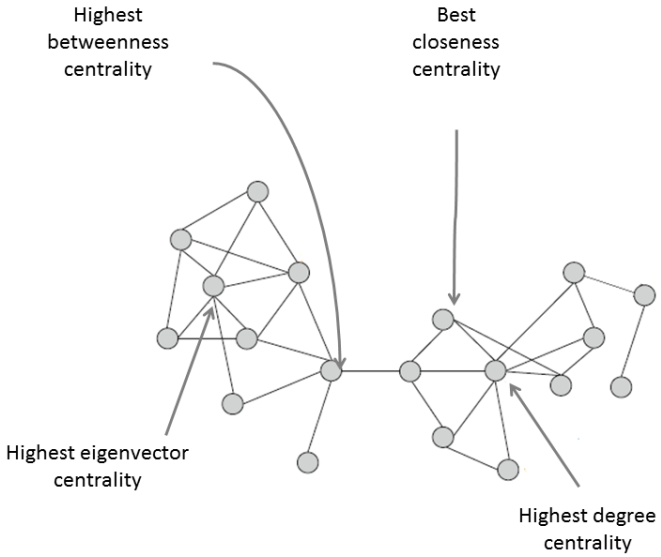


*Figure 7. Brain networks can be described as graphs consisting of nodes (representing brain regions) and edges (describing functional connectivity). The circles denote nodes, and the links between them are edges. Nodes with the highest centrality are different, depending on the chosen centrality measure.*

The relationship between brain topology and cognitive function is relatively unexplored. The simplicity and generalizability of graph theory turns it into an appropriate method to address this relationship. The method provides a systematic approach to investigate how the organization of communication patterns is linked to cognition. Using different graph indices for probing the organization of communication patterns of a complex brain network may give us a better understanding of cognitive functions and ultimately serve as a biomarker of psychiatric brain disorders as well as of neurodegenerative diseases (Bassett et al., 2008; Bullmore and Sporns, 2009; Supekar et al., 2008; van den Heuvel et al., 2010).

Studying the organization of functional connections in the brain via graph theory is not without difficulties. The number of nodes and the average degree of the network are shown to influence graph measures, which is of particular importance for direct comparisons of graph measures derived from different networks (van Wijk *et al.*, 2010). Therefore, the first obstacle in using graph theory for exploring brain function concerns the very definition of nodes. A typical suggestion is to use brain atlases in which regions of interest are defined based on macroscopic landmarks (Desikan *et al.*, 2006; Tzourio-Mazoyer *et al.*, 2002). Random parcellation of GM into contiguous nodes with equal sizes is another proposed method (Zalesky *et al.*, 2010). However, there are brain atlases based on structural (Anwander *et al.*, 2007) and functional (Craddock *et al.*, 2012; Power *et al.*, 2011; Yeo *et al.*, 2011) connectivity patterns, which have gained considerable success. In particular, multivariate decomposition of fMRI data using methods such as ICA (Kiviniemi *et al.*, 2009; Yu *et al.*, 2017) is being increasingly applied as a node-detection technique. Because of age-related spatial reorganization of RSNs and changes in the location of functional regions (Chan *et al.*, 2014; Goldstone *et al.*, 2016; Littow *et al.*, 2010; Sohn *et al.*, 2015), as well as disease-related brain variability (Toga *et al.*, 2001), additional care must be taken in using atlases from young healthy subjects in studies involving elderly persons or patient samples.

Additionally, we note that functional graphs are often very dense because they are created based on the statistical dependencies among regional time series. Therefore, graph analysis will mostly benefit from applying a threshold to maximize the separation of putatively real links from spurious and noisy ones. However, the choice of an appropriate threshold is up to the analyst and must be made with caution. Additionally, applying a fixed threshold to the connectivity matrices of individuals with different average levels of connectivity, leads to differences in the connection densities of individual networks. For example, previous research reported lower overall FC in both schizophrenia and autism patients compared with controls (van den Heuvel *et al.*, 2017). Applying the same threshold (for example 0.2) to patients and controls, results in higher network density for the controls. Since graph measures are mostly sensitive to the number of edges as captured by network density, this variation causes a serious problem.

An alternative approach is to use density-based thresholding strategy, to achieve the same number of edges in all individuals by allowing the value of absolute threshold to vary from network to network. Following on from the previous example, for a fixed network density,

the value of absolute threshold will be higher for the control network as compared with the patient one. Therefore, the patient's network comprises more correlations of low-value, which possibly represent spurious links, leading to for example artificially inflated and biased differences in network efficiency and clustering. Preserving a higher proportion of potentially spurious links may have the consequence of rendering the network topology more random (Fornito *et al.*, 2016; van den Heuvel *et al.*, 2017). Particularly, the network topology in schizophrenia and some other psychiatric disorders have been shown to appear more random compared with healthy individuals, which may only be induced through density-based thresholding strategy. In the present case, untangling differences in FC weights from differences in network measures can be very difficult (Fornito et al., 2016; Rubinov et al., 2009; van den Heuvel et al., 2017). In conclusion, these approaches have their own benefits and pitfalls, and therefore none of them gives rise to a fully unbiased analysis.

## 5.2 TEMPORAL NETWORKS

*"Change is the only constant in life."*

*— Heraclitus*

So far, we explained how systems consisting of different interacting units can be described as a graph, where each node symbolizes one single unit of the system and each link represents a certain type of relationship between the units. However, in a real-world networked system, the interactions among units are seldom persistent over time and therefore a static adjacency matrix seems an oversimplifying approximation. Instead, we need to represent a time-evolving networked system as a time-series of matrices namely time-varying (dynamic) graphs or temporal networks.

In general, adding the time dimension to the graphs introduces complexity to both visualization of the network and exploiting the relevant information in the form of different measures to characterize the network. If we deal with small, sparse networks, the temporal network can be represented as a sequence of edges or contacts over time (for example see Figure 1a and 1c in (Sizemore and Bassett, 2018)), however this visualization technique becomes less appropriate as the number of time-points increases. Temporal networks with long time-series are sometimes illustrated as a time-aggregated graph in which information about the time dimension is neglected (for example see Figure 1b in (Sizemore and Bassett, 2018)).

The key step in the network analysis is extracting informative measures to help us understand and describe how network units are organized and exchange information. Graph theory is simply applicable to the networks with time-varying edges, if we ignore the temporal dependencies between consecutive graphs ordered in time and just attach to the previously defined metrics which were all based on the node adjacency. Accordingly, we can track changes in the network properties by investigating time-varying graph measures which are computed at each time-point independent from the rest of time-points (Sizemore and Bassett, 2018; Sporns, 2018; Zalesky *et al.*, 2014). Following the aforementioned approach, several

studies have found interesting associations between network characteristics and time, like a time-varying nature for the modular organization of functional brain networks during resting state (Fukushima *et al.*, 2018; Jones *et al.*, 2012; Zalesky *et al.*, 2014). Another study further investigated spatiotemporal properties of time-varying brain network in the intervals with low and high modularity, and suggested that fluctuations in modularity of resting-state brain network may be rooted in the differences in the tendency of the DMN to dissociate from task-positive networks (Fukushima *et al.*, 2018). Furthermore, regional efficiency has been shown to vary over time, in a sense that brain dynamics gives rise to short-term spontaneous increases in the global efficiency of the network ensuring a balance between efficient information exchange and metabolic costs (Zalesky *et al.*, 2014).

Although this intuitive extension of measures as a function of time may seem a reasonable method for many nodal and global measures like clustering coefficient efficiency, it is not generally applicable (Sizemore and Bassett, 2018). Additionally, characterizing the network structure and evolution only by means of the metrics which are defined based on the nodal adjacency, neglecting the temporal dependencies of the sequential graphs, fails to explicitly account for the time dimension and leads to inaccuracies in the identification of network reconfigurations. Therefore, there have been considerable attempts to extend the concept of adjacency for the case of temporal networks by including time as one additional dimension in the definition of the graph (Holme and Saramäki, 2013, 2012; Nicosia et al., 2013; Sizemore and Bassett, 2018; Thompson et al., 2017). In a temporal network, the term "edge" is often substituted by the term "contact", whose definition requires the time-point as an additional restriction on connectivity.

In the graph theory, the reachability between two nodes is related to the concept of walk or path, where a walk or path is defined as an ordered sequence of edges connecting two nodes in a contiguous manner, depending on the adjacency of nodes. Given that in a temporal network the nodal adjacency may vary as a function of time, the nodal reachability is redefined in terms of time-respecting paths. Specifically, a time-respecting path is a sequence of contacts $\{(Node_i, Node_j, t_1), (Node_j, Node_k, t_2), (Node_k, Node_m, t_3), \ldots\}$, which agrees with the arrow of time, meaning that it does not break the contiguity of the sequence in time.

We note that a time-respecting path is not necessarily transitive (as it was in static graphs), meaning that the existence of a path from $Node_i$ to $Node_k$, and also a path from $Node_k$ to $Node_z$, is not an indication of the existence of a path from $Node_i$ to $Node_z$. Correspondingly, $Node_i$ is temporally connected to $Node_m$ only if a time-respecting path traveling from $Node_i$ to $Node_m$ exists. It is worth mentioning that because of the importance of temporal ordering, this type of connectedness is not symmetric. That is, if $Node_i$ is temporally connected to $Node_m$, in general $Node_m$ can be either temporally connected or disconnected to $Node_i$. If there is a two-way temporal connection, these two nodes are said to be strongly connected.

Studying reachability of a node based on the notion of time-respecting paths allows us to define two key time-varying features for an individual node, namely the source set and influence set. At any chosen specific time-point, the source set of a node is defined as the

collection of all nodes that can reach a given node of interest through time-respecting paths, within a given time interval. Additionally, again at any chosen specific time-point, we can define the set of influence of a node as the collection of all nodes that can be reached from that particular node via time-respecting paths, beginning no earlier than a given start time. The size and composition of the source and influence sets of an individual node, can provide useful information about the function of that particular node in information integration and sharing.

The duration of the path, computed as the time difference between the last and first contacts, is known as the temporal path length. The temporal path length of the rapidest path connecting two nodes (the shortest traveling time between those two nodes) is known as their latency (temporal distance). Correspondingly, temporal betweenness centrality of an individual node is defined as the fraction of fastest paths traveling through that particular node. Similarly, various graph measures have been redefined and many new measures have been introduced to characterize for temporal networks. We refer the readers to the detailed description of measures related to the concept of temporal networks (Holme and Saramäki, 2012; Nicosia *et al.*, 2013; Sizemore and Bassett, 2018).

## 5.3 COMPLEX NETWORKS

*"I think the next [21st] century will be the century of complexity."*

*— Stephen Hawking*

Many of the systems around us are complex systems. Complex systems are often characterized by a collection of components whose dynamic interactions (which are mostly local) with each other gives rise to the emergence of global properties that cannot be inferred from properties of individual system components. Therefore, a complex system has a non-linear dynamic nature and we cannot understand it in the reductionism frameworks like by using superposition principle (Mora-Lopez, 2009).

The popular phrase by Aristotle "The whole is more than the sum of its parts" aptly defines the concept of such an emergent behavior in complex systems. Complex systems are difficult to understand or analyze, because describing the whole system's function (its collective behavior) requires understanding the behavior of each individual component in relation to the other components (Bar-Yam *et al.*, 1998). Accordingly, it has been previously recommended to use the term "interdependent" instead of "interconnected" for describing the components of a complex system, in order to highlight the influence one component has on another as an essential property of the dynamic systems (Bar-Yam *et al.*, 1998; De Bot *et al.*, 2007).

It might be worth to highlight that the word "complex" is not interchangeable with the word "complicated", as it is inherently more challenging and unpredictable, with no necessity to have so many components (Rogers, 2008). A double pendulum which is simply made by attaching one pendulum to the free end of another pendulum is one of the simplest examples of a complex system, showing chaotic dynamics. Such a complex behavior which is resulted from the interaction between two pendulums seems very different and often unexpected from

properties of each individual pendulum. Systems with chaotic dynamics are often deterministic systems whose behavior can theoretically be predicted, but it is extremely sensitive to the initial conditions. Therefore, in practice, their behavior is predictable only for a short time which varies by the accuracy in measuring the initial condition. Indeed, unavoidable uncertainty of measuring instruments makes the long-term prediction of chaotic behavior impossible (De Bot *et al.*, 2007).

Complexity science deals with understanding how a collection of locally-collaborating components, can spontaneously self-organize to exhibit a functioning whole. Think of the complex flying patterns formed by the bird flocks in sky. It seems like an amorphous moving creature which is constantly changing in shape, but once you get closer you will see hundreds of birds each one acting as an individual agent (component) in this complex system. Indeed, complex self-organization characteristic has been observed in different types of swarms, although they work through very simple rules of behavior – like locally interacting with their neighbors at small scales, avoiding collision and trying to align themselves to the average direction of the agents in their neighborhood. When confronted with a predator, they scatter away at random and attract to each other afterwards. Although this constant splitting and reforming seems like an effortful act being made by each individual aiming to cooperate, all this comes out of their selfish behavior to save themselves. Swarming is indeed an advantage for every individual, as there are many eyes to spot an attack, and in the case of any danger, waves of panic will quickly propagate over long distances (Mora-Lopez, 2009; Pikovsky *et al.*, 2002; Strogatz, 2004).

Since complex systems are dynamical systems, they can be studied in terms of the temporal changes of their states. As discussed in the previous section, the state of a system is a set of variables that is capable to best characterize the system at any time. Temporal changes in the states of a complex system are typically non-linear, meaning that the change is not directly proportional to the system's current state or changes in the environment, causing different change rates depending on their states and their environment (Bar-Yam *et al.*, 1998; Mora-Lopez, 2009).

Besides the nonlinear dynamic character of the system, the architecture of the network is another important property that characterizes a complex system (Mora-Lopez, 2009). There have been several attempts to generate networks with the similar topology to complex networks in the real-world. For example, Barabási and Albert suggested an algorithm for generating networks with the scale-free property, as approximately seen in some natural and human-made complex systems (Barabasi and Albert, 1999; Barabási, 2016; Broido and Clauset, 2019). The network growth in the Barabasi-Albert model has been based on preferential attachment theory, so that nodes that enter the network with a higher probability will attach to the nodes with more connections. Degree distribution of these networks can be estimated by a power law, rather than binomial or exponential distributions. Most nodes in a power-law distribution have a low level of degree, although there are some nodes with high connectedness, too. Therefore, we cannot select a single node to represent the others,

providing an estimate of the average degree of the other nodes. Networks following power-law degree distribution are called scale-free networks, because they do not have any characteristic scale (Barabasi and Albert, 1999). In regular and random networks, the breakdown of the system in face of random failure is not a gradual process; rather, there is an abrupt phase transition from a large connected component to fragmentation, as assumed by the inverse-percolation theory (Stauffer and Aharony, 1994). However, the fragmentation process in the presence of random failures in scale-free networks is gradual. This characteristic makes them remarkably robust compared to random or regular networks. However, they are more vulnerable than other networks to selective attacks. Removing nodes with the highest degree (i.e. hubs) may promptly break the network into small disconnected clusters (Barabási, 2016).

Every individual component of a complex system can also be a whole new system, a characteristic that is known as multi-scale structure. Therefore, network science theories and approaches applied in such cases, need to be further developed to account for interdependencies between different scales (Betzel and Bassett, 2017; Michelson *et al.*, 2018).

Computational modeling of nonlinear dynamics provides us with the opportunity to deepen our understanding of how complex systems are structured and change with time (Bar-Yam *et al.*, 1998; Mora-Lopez, 2009).

### 5.3.1 Human Brain as a Complex Network

*"Overall, the human brain is the most complex object known in the universe – known, that is, to itself."*

*— Edward Osborne Wilson*

Human brain is an extraordinary complex system, in which global dynamical states have been brought about by the activation of interconnected neuronal populations, giving rise to complex processes involved in perception and cognition (Mesulam, 1998; Sporns, 2004). Understanding the principles that underlie complex structures of cortical organization has been proven to be difficult. Segregation and integration are two dominant principles of functional organization of the cerebral cortex that play fundamental roles in neural processing. Advances in neuroimaging approaches have provided overwhelming evidence to support the view of functional specialization at multiple spatial scales as a fundamental organizational motif (Sporns, 2004; Tononi *et al.*, 1998). Information conveyed by individual activities of functionally specialized areas must be rapidly evaluated and integrated into a unified coherent scene. Previous findings suggest that, similar to functional specialization, rapid integration of information occurs at multiple spatial and temporal scales, even when we are asleep (Tononi *et al.*, 1998). The structural basis for the functional interactions underlying the integration of neural activity between specialized regions has been formed by anatomical pathways, which are found at all levels of scales, including the long-range ones linking remote brain regions across the cerebral cortex. Although structured anatomical paths are

central to interactions between specialized components and generating an organized whole activity, we still have limited knowledge of the emergence of brain dynamics from the underlying anatomical connectivity (Jirsa and Kelso, 2004; Tononi *et al.*, 1998).

Understanding the architecture of the human brain as an integrative network with flexible neural dynamics is an increasingly attractive topic in neuroscience. Network science creates a platform to study information integration in the brain, how such integration is altered across different conditions, and may have implications for understanding cognitive problems and brain disorders. Brain-network analysis was catalyzed by remarkable advances by the advent of neuroimaging techniques (both in acquisition and analysis of imaging data), which made it possible to explore connectivity patterns in the brain more comprehensively. Research based on FC analysis gave us new insights into both local and global organization of communication patterns in the brain. For example, there is some evidence suggesting that resting-state FC in the human brain has a combined small-world and scale-free organization (Eguíluz *et al.*, 2005; Fornito *et al.*, 2016; van den Heuvel *et al.*, 2008). On the other hand, some studies have argued that human brain networks have exponentially truncated power law degree distributions, implying relatively less probabilities of hubs with large connectendness (Achard *et al.*, 2006; Aerts *et al.*, 2016). This characteristic makes brain networks more resilient to targeted attacks on the central regions than a comparable scale-free network (Achard *et al.*, 2006; Aerts *et al.*, 2016).

A number of experimental studies support the critical brain hypothesis, according which the collective dynamics of large neuronal networks works near the critical point of a phase transition. In the immediate vicinity of the critical point, the whole-brain activity would be continuously transitioning between two phases associated with either rapidly reducing and dying activity, or amplifying over time. Particularly, resting-state networks are shown to operate at the vicinity of critical point, where there is continuous switching between two network states, characterized by uncoordinated cortical activity (lack of integration) and coherent cortical activity (lack of segregation). Regarding the proposed role of criticality in resting-state brain dynamics, there is a body of evidence from EEG, magnetoencephalography (MEG) and fMRI studies indicating a dynamic balance of integration and segregation for large-scale resting-state systems, near the critical point. It is also suggested that a slight incursion away from the critical regime may be required in cognitively demanding tasks (Cocchi *et al.*, 2017).

Additionally, recent understanding of the multiscale nature of the brain is one of the new horizons which have opened in the field (Bassett and Siebenhühner, 2013). Today, we know that our brain with about 100 billion neurons is organized over multiple scales of space and time (Betzel and Bassett, 2017; van den Heuvel and Hulshoff Pol, 2010). Characterization of networks over multiple spatial scales refers to their elements that may range from cells to large-scale networks. The concept of multiple temporal scales refers to the precision, varying from milliseconds (Khambhati *et al.*, 2015) to the entire lifespan (Zuo *et al.*, 2010). In parallel, topological scales of network analysis vary from individual nodes to the whole

network (Betzel and Bassett, 2017; Bullmore and Sporns, 2009; Rubinov and Sporns, 2010). Integration of neural activity across multiple scales gives rise to complex cognitive functions.

It is previously argued that network science requires multi-scale and multi-modal approaches with the capability of forming bridges between different scales in order to link neural activity across scales (Betzel and Bassett, 2017; Michelson *et al.*, 2018). Thus far, the mechanisms that unify neural activity across different spatiotemporal scales are to a large extent unknown (Cocchi *et al.*, 2017).

The framework of network science has revealed higher-order organization patterns, such as "rich clubs" which may direct us to a kind of unifying mechanism cross scales. Indeed, the constellation of highly connected hub regions that form an interconnected rich-club supports a core-periphery organization of the brain network dynamics which is characterized by multiple temporal scales. In this organization, a set of hub regions, largely operating at slow frequencies, acts as an integrative core, whereas peripheral regions such as the visual and sensorimotor systems operating at faster frequencies introduce stimuli related variability in the system (Bassett and Siebenhühner, 2013; Cocchi *et al.*, 2017; Gollo *et al.*, 2015). Equally important, phase-amplitude cross-frequency coupling is a suggested mechanism for communication between brain areas (Canolty and Knight, 2010; Canolty *et al.*, 2006; Florin and Baillet, 2015; Szczepanski *et al.*, 2014). In this case, a previous study using magnetoencephalography imaging during rest indicated that the resting-state networks emerge from cross-frequency coupling between the phase of a low-frequency oscillation and the high-frequency oscillation's amplitude in neural oscillations across the brain (Florin and Baillet, 2015; Szczepanski *et al.*, 2014). Notably, several studies have demonstrated that the synchronized phase-amplitude coupling operates through a physiologically plausible mechanism (Cardin *et al.*, 2009; Ray and Maunsell, 2011; Szczepanski *et al.*, 2014).

## 5.4 COMPUTATIONAL MODELING OF BRAIN NETWORK

*"Mathematicians do not study objects, but relations between objects. Thus, they are free to replace some objects by others so long as the relations remain unchanged. Content to them is irrelevant: they are interested in form only."*

*— Henri Poincaré*

Studying a complex system often begins with a set of models that are capable of capturing some aspects of the dynamics in that particular system (Bar-Yam *et al.*, 1998). Graph-theoretical representation of brain network, by means of either static or time-varying (dynamic) measures of FC, has gained considerable ground in neuroscience (Bassett and Sporns, 2017; Bullmore and Sporns, 2009; Fornito *et al.*, 2013). Network mapping by comprehensive recording of connections in the brain system have consistently revealed nonrandom topological attributes like highly connected hub regions, and even more complex organizational features such as hierarchical organization (Bassett and Sporns, 2017). Abstract characterization of brain network based on graph theory mainly aims to summarize the empirical data in terms of some graph measures in order to describe the network organization.

Therefore, it can be categorized as a more descriptive type of modeling, with very limited predictive usages. Even though simple generative principles may in parallel be employed for making statistical comparisons, as a complement for descriptive accounts of network topology (Rubinov and Sporns, 2011; Sporns, 2018), more advanced generative models (so called mechanistic models) of brain responses are required to illuminate the emergence of the brain dynamics and FC patterns based on a network of structural couplings and for a further understanding of their breakdown in disease (Cabral *et al.*, 2014; Deco and Kringelbach, 2014; Deco *et al.*, 2011; Honey and Sporns, 2008). Nowadays, with access to greater computational power, it is possible to build forward models which can help us explain and predict empirical functional network data by simulating the activity of neural elements and their interactions based on the biophysical properties of neural elements that are linked via structural links (Bassett and Sporns, 2017).

The interplay between the structural connectome and the dynamics of the brain, yet to the large extent unknown, is said to underlie all different functions from consciousness and perception to learning, memory, and movement (Deco *et al.*, 2008). Accordingly, mathematical modeling of the brain network dynamics has launched an initiative to address the key questions regarding to the role of brain's structure in shaping FCs within the brain and also the emergence of complex brain dynamics (Breakspear *et al.*, 2010; Cabral *et al.*, 2014; Fink, 2018; Ritter *et al.*, 2013; Roberts *et al.*, 2018). This is leading to expectations that whole-brain computational modeling is a good entry point for understanding cognitive impairments and brain disorders at a causal mechanistic level, and ultimately designing goal-directed therapeutic interventions based on appropriate targets (Deco and Kringelbach, 2014).

Computational modeling based on non-linear differential equations helps neuroscientists understand the fundamental mechanisms that underpin neural dynamics, at different space–time scales (Breakspear *et al.*, 2010; Deco *et al.*, 2008; Sporns, 2018). There is a wide range of candidate models commonly used in neuroscience, from simple algebraic forms to complex networks of multi-compartment neurons connected based on a synaptic map. Detailed computational models of individual spiking neurons, like different types of electrical input–output membrane voltage, have helped to investigate specific mechanisms and generate spiking and bursting behaviors replicating electrophysiological observations. However, systematic exploration of such complex models is hampered by increasing number of model parameters (Breakspear *et al.*, 2010).

In order to investigate how interactions between locally generated oscillations at different cortical regions give rise to the emergent dynamics at the level of whole brain, we need to think beyond microscopic firing of single neurons and instead think about mesoscopic behavior observed for neuronal populations (Deco *et al.*, 2008).

Accordingly, one solution is considering neural mass models by which the complexity of neural models is reduced to a set of nonlinear differential equations modeling the activity of a population of neurons (Cabral *et al.*, 2014; Deco *et al.*, 2008). Computational modeling of whole-brain network dynamics through reduced neural mass models, mostly attempts to

unravel the fundamental laws governing spontaneous emergence of resting-state fluctuations, in order to generate neural activity and dynamics from simple structural ingredients (Breakspear *et al.*, 2010; Sporns, 2018). Using neural mass models coupled according to the realistic structural connectivity has been attracting a growing body of research for the understanding of resting-state dynamics (Breakspear et al., 2010; Cabral et al., 2014, 2011; Deco et al., 2008). Parsimonious models in general can provide central targets for therapeutic interventions and therefore they can have important implications for the diagnosis and treatment of brain disorders (Durstewitz *et al.*, 2018).

A number of studies have tested multiple oscillator types to describe the local dynamics of each brain region in the neural mass modeling, including the Stuart-Landau oscillator. The Stuart-Landau oscillator is a nonlinear oscillating system near the Hopf bifurcation, capable of expressing both noisy asynchronous dynamics and oscillatory behaviors, and therefore it is thought of as the principal model to describe amplitude dynamics (Röhm, Lüdge, & Schneider, 2018). When coupled together at the optimal working point, the collective behavior of interacting oscillator systems has been shown to reproduce the key structures of brain dynamics (Deco, Kringelbach, Jirsa, & Ritter, 2017; Freyer et al., 2011). A previous study which used these oscillators for modeling resting state dynamics in fMRI have found that the best fit of this model to the neuroimaging data occurs at the brink of bifurcation (transition from fixed point to oscillating behavior), where the steady state solutions and the periodic oscillations co-exist (Deco *et al.*, 2017). This type of behavior is called multistability (Deco *et al.*, 2017; Freyer *et al.*, 2011; Tognoli and Kelso, 2014). A system with multiple co-existing stable states or attractors which requires external input to cause switching between stable states, is called a multistable system (Kelso, 2012). Apart from multistability, this model captures another key feature of a healthy brain dynamics as well, namely high metastability. Metastability refers to the simultaneous realization of two competing tendencies (existence of a form of winnerless competition) to synchronize and desynchronize, achieved by spontaneous shifting between unstable states or transient attractor-like states (Kelso, 2012). Additionally, models with Hopf bifurcation are particularly well-suited for simulating the effects of GM lesions (Deco et al., 2018), with no need to remove any structural link in the network.

An increased degree of reduction of a neural-mass model to a phase oscillator has been attracting great attention in computational neuroscience (Breakspear *et al.*, 2010; Cabral *et al.*, 2011), supported by both experimental and theoretical studies (Brunel and Wang, 2003; Hoppensteadt and Izhikevich, 1997; Schuster and Wagner, 1990). Indeed, applying more abstracted models not only further enhances analytical tractability, but also may better explain common fundamental mechanisms that may underpin a variety of diverse anatomical and physiological processes (Breakspear *et al.*, 2010). In terms of describing coupled oscillator systems, the simplest model achievable is the Kuramoto model (Kuramoto, 1984). Kuramoto suggests that activity of a local system (e.g., a neuron or a brain region) can be adequately characterized only by its phase (Figure 8). Kuramoto model is built based on several assumptions, including the existence of weak coupling between oscillators, as well as

the dependency of interactions on the sine of phase difference between each pair of oscillators.

In order to describe the emergence behavior in a system of oscillators, as described in the framework of Kuramoto problem, consider N oscillatory units coupled based on the simplest network structure (all to all with equal strength). The state of each unit at time $t$ is described only by one state variable, representing the phase of its oscillation ($\theta_i$). The state space of an individual unit can be illustrated as the circumference of a unit circle, and each unit's state is denoted by a point in the state space (Figure 8). We assume that oscillator frequencies are randomly selected from a distribution with a single local maximum.

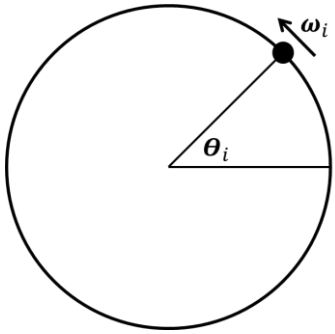


*Figure 8. An individual oscillator represented by its circular phase.*

According to the most common form of the Kuramoto model, the phase of unit $i$ at time $t$ ($\theta_i$) obeys the following dynamical equation:

$$\frac{d\theta_i}{dt} = \omega_i + \frac{k}{N}\sum_{j=1}^{N} \sin(\theta_j - \theta_i)\,, \quad i = 1, \dots, N$$

In this case, oscillators are coupled together according to the second term in this equation, where $k$ is a constant value representative of the magnitude of the coupling. The two terms in this equation are competing with each other. To clarify, assume a specific case in which the global coupling constant is set to zero ($k = 0$). Additionally, assume that all these oscillators are initialized in synchrony with each other (meaning that their phases are all gathered together as illustrated in the right phase space of Figure 9). After these oscillators are coupled altogether, they all go around at different rates spreading out over $2\pi$, reducing the synchrony in phase (similar to what we see in the left phase space of Figure 9). However, in the case of a nonzero value for the global coupling constant, $\theta_i$ increases when the values of $\theta_j$are bigger than $\theta_i$ (i.e., oscillator $i$ goes faster than its natural frequency to catch up oscillator $j$), whereas $\theta_i$ decreases as the values of $\theta_j$are smaller than $\theta_i$ (i.e., oscillator $i$ goes slower than its natural frequency to reach oscillator $j$ which is behind it). For this reason, the second term in the equation is said to promote synchrony in phase. Kuramoto introduced complex order parameter to capture the level of macroscopic synchrony of the collection of N phase oscillators. The order parameter ($R$) is simply resulted from averaging the complex numbers representing the phase of N oscillators on the unit circle. Therefore, it can be written as:

$$R = \frac{1}{N}\sum_{i=1}^{N} e^{i\theta_i} = r\, e^{i\psi}$$

Importantly, the magnitude of the order parameter ($r$) describes the global phase coherence of the system at each time-point. As illustrated in Figure 9, when the phases of oscillators have large circular variance (meaning that they are uniformly spread out over $2\pi$), the global phase coherence approaches zero, whereas it approaches one when all the oscillators are moving nearly in phase (Breakspear *et al.*, 2010). Usually, the global dynamic behavior of the ensemble of oscillators is described by the mean and standard deviation of the magnitude of the order parameter across all time-points, respectively called the global synchrony and global metastability of the whole system (Cabral *et al.*, 2011; Váša *et al.*, 2015).

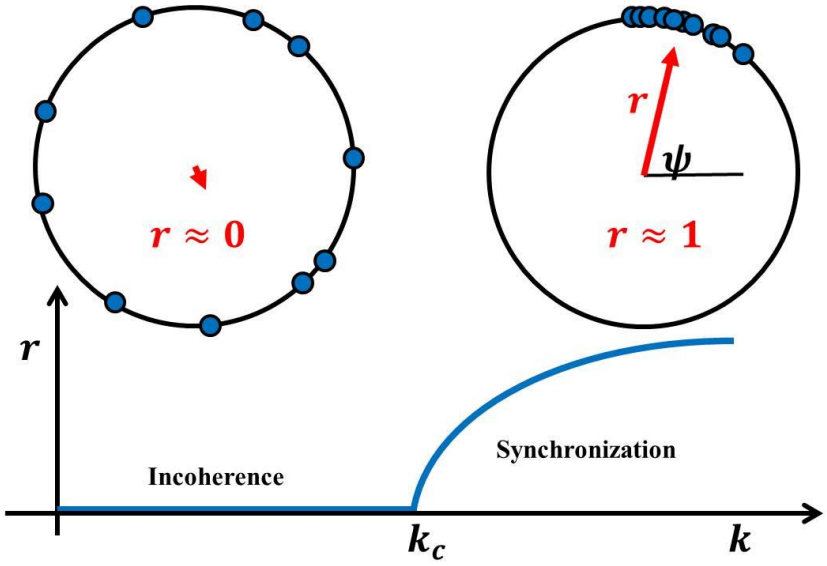


*Figure 9. Order parameter measuring the global coherence of the system. As the figure illustrates, the level of synchrony in population stays weak until k passes a critical coupling strength ($k_c$). Above the critical coupling strength ($k_c$), oscillators starts to synchronize and r monotonically increases.*

Using the Kuramoto model, whole-brain network dynamics can be simulated by a number of phase oscillators which are coupled to each other based on the underlying anatomical skeleton (Breakspear *et al.*, 2010; Cabral *et al.*, 2011). The Kuramoto model has been proven capable of showing non-trivial collective dynamics and synchronization behaviors, as observed in a wide variety of fields, including biological systems. Additionally, many generalizations of the Kuramoto model (with delays and complex coupling structures) have been proposed to analyze a wide variety of complex dynamics (Acebrón *et al.*, 2005; Breakspear *et al.*, 2010; Lee *et al.*, 2009; Yeung and Strogatz, 1999).

Previous attempts to model the resting-state oscillations using the well-studied Kuramoto model suggested using a generalized version which takes into account the delays for the interactions between oscillators. Specifically, they reported that the best fit of Kuramoto model with the neuroimaging data occurs for sufficiently large coupling delay, in the critical border between asynchrony and partial synchrony, representing an intermediate regime between incoherence and global synchronization (Cabral *et al.*, 2011), where metastable partial synchronization occurs.

Inferring subject-specific model parameters from the neuroimaging data is of particular interest for diagnostic and therapeutic applications, such as pre-surgical assessment of the effects of various neurosurgical approaches to optimize the surgical strategy for any particular individual (Aerts *et al.*, 2018; Stephan *et al.*, 2015). There are several studies showing differences in parameter estimates across drug conditions (Moran *et al.*, 2011) or in disease (Saenger *et al.*, 2017). For example, in a previous study where a set of coupled normal Hopf oscillators was recruited, bifurcation parameters of individual regions were separately estimated by fitting the normalized power of each intrinsic frequency band to the normalized power of its respective empirical signal. They found that brain regions in patients with Parkinson's disease were mostly characterized by negative bifurcation parameters demonstrating noisy behavior corresponding to an asynchronous firing of neurons (Saenger *et al.*, 2017).

Notably, simulating the effects of brain network failures and perturbations may become a useful tool for predicting the course of disease as well as designing goal-directed interventions such as presenting sensory stimuli and interventions like applying transcranial magnetic stimulation (Aerts *et al.*, 2016; Weerasinghe *et al.*, 2018). Moreover, a previous study showed that a mathematical model of the brain oscillations is helpful in designing an optimal stimulation strategy by showing promising results for a new closed loop method of deep brain stimulation which was based on the ongoing brain activity (Weerasinghe *et al.*, 2018).

Computational modeling may also play an important role to better understand why certain brain lesions cause cognitive and physical impairment that may become more severe over time while other lesion patterns have a much a better long-term outcome (Aerts *et al.*, 2016). Indeed, some local brain lesions may initiate a cascade of failures and lead to disease, whereas others do not. In a broad sense, different brain diseases may be modeled as a cascade failure. For example, in patients with Alzheimer's disease the deposition of amyloid-β plaques which cause synaptic disconnection and neuronal cell death (Mokhtar *et al.*, 2013), may be modeled as a failure in brain networks, causing a cascade of failures. Neuronal death and disconnection in patients with Traumatic Brain Injury (TBI) may also be modeled in terms of compromised brain networks, which in some cases may lead to a cascade of failures. Interestingly, there is growing evidence that amyloid-β plaques may be found in the brain of TBI patients, even in children. The plaques observed are strikingly similar to those found in Alzheimer's disease, although TBI-associated plaques may have appeared within hours

following the injury (Esopenko and Levine, 2015; Johnson *et al.*, 2010; Lye and Shores, 2000; Sundman *et al.*, 2014). In addition, the process of cognitive aging may go faster in the subjects with a history of remote TBI (Esopenko and Levine, 2015). Generally speaking, to avoid cascade failures in a system, we need to understand the structure of the network supporting the propagation of the cascade. In addition, we must understand the dynamic processes in the networks. The interplay between the structure and dynamics of a network plays an important role in a system's ability to survive failures and attacks (Albert *et al.*, 2000). By perturbing different network nodes and subsequently measuring how the system responds to the induced perturbations, we can acquire important information on the underlying association between the network structure and dynamics. Large-scale computational models are uniquely suited to address questions regarding the relationship between the structural backbone and the dynamics of brain activity and also by contributing to the modeling of lesion propagation; they in turn improve both predicting the course of disease and designing therapeutic procedures.

# 6 CHAPTER 6: RESEARCH REPORTED IN THIS THESIS

## 6.1 INTRODUCTION — OVERAL AIMS

The key aims of this thesis were to apply and develop novel approaches for quantification of resting-state FC in healthy aging and ADHD patients, as well as computational modeling of whole brain oscillations based on only the structural brain connectome.

In the first two studies, we hypothesized that individual differences in FC are associated with cognitive differences. With a particular focus on the DMN, we explored whether individual differences in DMN FC are associated with differences in episodic memory in both age-homogenous and age-heterogeneous samples. The key aims of the first two studies were: (1) to investigate age-related changes in the functional architecture of the medial temporal lobe (MTL), a subsystem of the DMN, and their links to perfusion and episodic memory decline in old age; (2) to examine the specificity of the association between FC of the DMN subsystems and episodic memory in old age.

In the third study, in an attempt to characterize FC patterns in ADHD, we decided to have a less reductionistic perspective. With a particular focus on the FCs of the DMN, we introduced a new method for extracting different stable configurations of FC patterns for the DMN, namely synergies. We aimed to explore dynamic configurations of DMN connections in healthy and ADHD cohorts.

In the fourth study, we proposed a novel macroscopic computational model of the brain oscillations for resting-state fMRI, by introducing the frequency dynamics into a system of coupled oscillators. Moreover, we investigated the effects of simulated GM lesions by applying an *in silico* perturbation protocol to the brain model. Therefore, my last study can be separated into two themes, (a) computational modeling, and (b) FC analysis.

## 6.2 DATASETS

This doctoral thesis has so far been based on four well-established data sets: the Betula project for Study I; the Cognition, Brain, and Aging (COBRA) project for Study II; and two open access datasets for Studies III and IV, namely the UCLA Consortium for Neuropsychiatric Phenomics and Human Connectome Project. A description of each data set is given below.

### 6.2.1 The Betula Project

Betula is an ongoing longitudinal study on aging, health, and cognition, conducted in Umeå, Sweden (Nilsson et al., 2004, 1997). The first wave of data collection was done in 1988-1990. Another five waves of data collection have then followed with five years apart. A total of 4500 individuals, randomly selected from the population registry, have participated across the waves of data collection. Participants were 25, 30, 35, …, 85 years of age, when first tested. A large longitudinal database has been built up, including data from an extensive battery of cognitive tests, health variables, demographic variables, and psychosocial

variables. The cognitive battery includes various cognitive domains, but is heavily focused on episodic memory. Episodic memory was measured in a similar way at 4 equally distributed time points across 15 years of study. The task battery consisted of free recall of sentences (verb + noun) with and without enactment, delayed cued recall of the same nouns, with and without enactment, as well as free recall of word lists. In addition, various brain measures including resting state fMRI, were collected at two different time points 5 years apart (Nilsson et al., 2004, 1997). At follow-up, cerebral blood flow (CBF) using 3D pseudo-continuous arterial spin labeling (pCASL) was measured. In Study I, resting-state fMRI, CBF, and a composite measure of episodic memory were used.

### 6.2.2 The COBRA Project

COBRA is an ongoing longitudinal multimodal imaging study that started in 2013 in Umeå, Sweden. The study follows a large cohort (n=183) of 64-68 years old adults randomly selected from the population registry in Umeå and the participants will be followed 3 times over a 10 year period. All individuals undergo an extensive test battery including central cognitive abilities (e.g. episodic memory, working memory, processing speed). A composite measure of episodic memory was made up of scores collected from word recall, number-word recall, and object-position recall tasks (Nevalainen *et al.,* 2015). Working memory was assessed by a combination of verbal, numerical and figural 3-back tasks. In addition, to measure perceptual speed, subjects were asked to compare letters, numbers, and figures. Each individual underwent a PET session using [11C]-raclopride to estimate DA D2/D3 receptor binding potential. Subjects also underwent MRI sessions during which brain structure and function were assessed. The data collection for the first wave has been completed, but participants will be tested at two additional measurement points, each separated by 4.5 years (for further information on the imaging dataset and cognitive battery, see (Nevalainen *et al.*, 2015; Nyberg *et al.,* 2016)). In Study II, resting-state fMRI data, as well composite measures for episodic memory, working memory, and perceptual speed were used.

### 6.2.3 UCLA Consortium for Neuropsychiatric Phenomics

In Study III, we utilized the open-access resting-state fMRI data from healthy controls (n = 121, age range: 21-50 yr) and subjects diagnosed with ADHD (n = 40, age range: 21-50 yr) from the University of California LA Consortium for Neuropsychiatric Phenomics study. Further details regarding the cohorts can be found in (Poldrack *et al.*, 2016).

### 6.2.4 Human Connectome Project

The primary data source for Study IV was the Human Connectome 500 subject release (Smith et al., 2013; Van Essen et al., 2012), which is publically available on the ConnectomeDB database (https://db.humanconnectome.org). We used resting-state fMRI data which was collected during 14.4 minutes with a temporal resolution of 0.72 s. The entire dataset consisted of 1200 image volumes.

Moreover, high-quality diffusion-weighted MRI data for the same 500 subjects from the HCP consortium (Glasser et al., 2013; Van Essen et al., 2012) was used for the streamline tractography on 68 gyral-based regions-of-interest (Yeh *et al.*, 2010), which were derived from cortical parcellation of subjects' T1-weighted images (Desikan *et al.*, 2006). This data-driven parcellation is also known as the 'Desikan-Killiany' cortical atlas.

## 6.3 PUBLICATIONS IN A NUTSHELL

### 6.3.1 Study I — Longitudinal Evidence for Dissociation of Anterior and Posterior Medial Temporal Lobe Resting-state Connectivity in Aging: Links to Perfusion and Memory

#### *6.3.1.1 Aims*

Cross-sectional studies on age-related alterations in resting-state FC of MTL have yielded inconsistent findings, suggesting that the effect of aging on posterior and anterior MTL is heterogeneous. Therefore, the key aims of this study were: to (a) investigate 5-year changes in FC of the anterior and posterior MTL subsystems of the DMN using longitudinal resting-state data from 198 participants; (b) examine whether there is any specificity in terms of the association between FC changes of MTL and episodic memory decline; and (c) explore the link between FC and CBF in distinct MTL regions to investigate whether age-related alterations in FC have metabolic implications.

#### *6.3.1.2 Methods*

Longitudinal resting-state fMRI data (two waves 5 years apart) were used as well as offline episodic memory assessment from 198 participants in the Betula prospective cohort study on memory, health, and aging (Nilsson et al., 2004, 1997). Episodic memory was calculated as a composite measure of five different task scores: (1) Free recall of short sentences including a command verb and a noun with and (2) without enactment by the subject (16 items each). (3) Delayed recall of nouns which were parts of the previously presented sentences with and (4) without enactment, with noun categories (e.g., animals and fruits) as cues (16 items each); and (5) Free recall of word lists with 12 unrelated nouns presented verbally. Episodic memory measurements over 15 years at 5-year intervals were applied to estimate individual slopes of memory change. The individual slopes of episodic memory change were estimated with linear regression of the cognitive scores against time of measurement.

In addition, at the follow-up session, CBF data was measured using a background suppressed, 3D pseudo-continuous arterial spin labeling (pCASL) sequence of MRI. In order to identify DMN subsystems, we applied ICA as implemented in the GIFT toolbox (Allen *et al.*, 2011; Calhoun *et al.*, 2001a, 2001b) to the preprocessed resting-state fMRI data. In brief, the ICA procedure was carried out as follows: (1) Temporal concatenation of intensity-normalized data for all participants, (2) Applying a minimum description length algorithm to estimate the number of components, (3) Using a two-step data reduction technique using principal component analysis (PCA1: 100 components; PCA2: 47 components), (4) Employing the

Infomax algorithm (Bell and Sejnowski, 1995) for optimal extraction of 47 group-level ICs, (5) Twenty times repetition of the last step with different initial points using ICASSO, which results in compact clusters of components in different runs, to estimate the reliability of the ICs, and (6) Performing back-reconstruction using the GICA3 method (Erhardt *et al.*, 2011) in order to estimate subject-level, time courses (TCs) and spatial maps (SMs). The value of each voxel in a subject-specific SM represents the degree to which that voxel is correlated with the given network's mean TC.

Subject-level TCs were detrended, despiked, and low-pass filtered (Butterworth, fifth-order, cutoff frequency equal to 0.15 Hz). The matrix of inter-network FC was estimated as Pearson's correlation coefficients between each pair of TCs. Then, estimated correlation coefficients were Fisher's r-to-z transformed. In addition, we computed two more ICA-based measures for the MTL components as follows: (1) A joint amplitude measure of each ICA-driven network (Allen *et al.*, 2012) was computed for each individual. This measure, which is a well-characterized indicator of the network's activation level, is simply the standard deviation of each component's TC scaled by the average value of the first 20 maximum intensities of the related component's spatial map. Motion parameters were regressed out from the TCs in addition to being detrended and despiked, and (2) Global connectivity of each ICA-driven network (Glahn *et al.*, 2010), computed as the first principal eigenvector extracted from the concatenated subject-specific SMs, indicates how close each subject's spatial map is to the mean spatial map.

Multiple regression analyses were performed to assess the link between change in voxel-wise FC of each MTL component and the level of decline in episodic memory. Sex and frame-wise displacement (FD) (Power *et al.*, 2012) as well as the baseline measures of episodic memory and FC were used as covariates of no interest in all statistical analyses.

#### *6.3.1.3 Results*

Thirty-two RSNs, including MTL and DMNs were identified. We found discrete MTL components along the longitudinal hippocampal axis (anterior MTL [aMTL] vs. posterior MTL [pMTL]). A 2 (aMTL vs. pMTL)*2 (baseline vs. follow-up) ANOVA revealed a significant interaction effect, suggesting a dissociation in the direction of age-related changes for aMTL and pMTL. More specifically, aMTL exhibited age-related decreases in FC, whereas pMTL reflected age-related increases. In addition, elevated FC of the posterior MTL was associated with level of decline in episodic memory. Further analysis of the CBF data, collected at the follow-up session, indicated an age-related CBF increase in posterior MTL, along with a positive association between age-related CBF increases and FC in posterior MTL. The latter finding suggests that age-related elevation of pMTL connectivity is a metabolically demanding process. Taken together, our results suggest that elevated pMTL connectivity accompanied by local increased blood flow is detrimental to episodic memory functioning.

### 6.3.2 Study II — The Retrosplenial Cortex: A Memory Gateway Between the Cortical Default Mode Network and the Medial Temporal Lobe

#### *6.3.2.1 Aims*

FC between the posterior DMN and MTL has been related to a variety of functions, including episodic memory, in both younger (Touroutoglou *et al.*, 2015; Vincent *et al.*, 2006; Voets *et al.*, 2014) and older (McCormick *et al.*, 2013; Mevel *et al.*, 2013; Salami *et al.*, 2014; Wang *et al.*, 2010) samples. However, there are other studies that failed to observe the aforementioned link (Andrews-Hanna *et al.*, 2007; Beason-Held *et al.*, 2009; Damoiseaux *et al.*, 2016; Vidal-Piñeiro *et al.*, 2014). Moreover, the central role of PCC and RSC in the functional architecture of the DMN is not fully understood. Thus, the aims of this study were to 1) examine the specificity in the FC between MTL and other DMN subsystems (e.g. PCC and RSC) in relation to memory; and 2) explore the role of RSC compared to PCC in terms of centrality in functional interactions within the DMN.

#### *6.3.2.2 Methods*

We used resting-state fMRI data collected from 183 healthy older adults (aged 64-68 years) in the COBRA project (Nevalainen *et al.*, 2015; Nyberg *et al.*, 2016). In addition, three cognitive composite scores representing different domains were used: episodic memory, working memory, and perceptual speed. Episodic memory was based on scores from (a) word recall, (b) number-word recall, and (c) object-position recall tasks. Working memory was determined by combining verbal, numerical, and figural 3-back tasks. Finally, a set of verbal, numerical, and figural comparison tasks was performed to assess perceptual speed.

ICA was applied to preprocessed resting-state fMRI data to identify DMN subsystems. Using ICA, we identified 5 DMN components. These included pDMN (mainly PCC [Brodmann Area (BA) 23] and precuneus [BA 31]), aDMN (medial prefrontal cortex [BA 32 and BA 10]), RSC (BA 30), and MTL. After DMNs were identified, additional pre-processing steps were carried out to remove the effects of motion and physiological noise from the data. Effects of motion (including 24 motion parameters), global signal, WM signal, and cerebrospinal fluid signal (extracted from unsmoothed images) as well as linear and quadratic trends were removed from the de-spiked data. Finally, spherical ROIs with a radius of 4 mm were centered on the non-artifactual local maxima of five DMN-related spatial ICA maps. Nodal-based FC between DMN subsystems was computed by averaging significant FCs ($ps < .05$, FDR corrected) among all nodal pairs belonging to different RSNs. Afterwards, inter-network FC of MTL to RSC and other cortical DMN areas were examined. Partial correlations were used to determine the relation between FC and the cognitive measures. FD, FD squared, age, and sex were used as covariates of no interest in all statistical analyses.

Using the MATLAB functions available in (http://wagerlab.colorado.edu/tools), multi-level mediational analysis (Kenny *et al.*, 2003) was performed to measure the average mediation effect of RSC on the MTL-cortical DMN link. As a control analyses, similar models were run with the pDMN (primarily PCC and precuneus) and parahippocampus (pHC) (Ward *et al.*,

2014) as the mediator variables. Further, the association between the mediational effects of RSC (i.e. standardized mediation coefficients) and episodic memory was investigated.

To compare the role of RSC to other DMN nodes in terms of centrality, graph-theory based analysis was carried out. Using this approach, the DMN was defined as a graph in which nodes represent different ICA-derived regions and edges represent interregional FC. The group-level thresholding method (de Reus and van den Heuvel, 2013) was employed to minimize false positive and false negative edges in the network architecture, at the expense of reducing inter-individual differences in FC. Finally, betweenness centrality measures were computed for the average connectivity matrix as well as for each subject separately.

#### *6.3.2.3 Results*

Among the DMN components, the degree of inter-network connectivity between MTL and RSC was reliably stronger than for MTL-pDMN and MTL-aDMN. In relating FC between MTL and the different DMN components to between-person differences in the episodic memory composite, we found a significant link to episodic memory for MTL-RSC FC.

A multi-level mediation approach showed a very strong positive mediational role of RSC such that MTL-cortical DMN FC improved when RSC was acting as a mediator. The degree of mediation effect of RSC was associated with episodic memory performance, suggesting that greater RSC mediation is beneficial to episodic memory. Further analysis applying graph-theory approaches on the signals extracted from the DMN regions showed the strongest betweenness centrality for the RSC, approving that a large proportion of shortest paths within the DMN travel through RSC. The results from this study suggest that RSC is the principal episodic memory gateway linking subcortical and cortical regions of the DMN among older adults.

### 6.3.3 Study III — Dynamic Synergetic Configurations of Resting-state Networks in ADHD

#### *6.3.3.1 Aims*

High distractibility and impaired executive functions such as working memory and cognitive control are the key features of a person with ADHD. Previous neuroimaging studies have reported ADHD-related dysfunctions for both cognitive control networks, namely the FPN and the CON, as well as the DMN. It has been hypothesized that impaired cognitive control in ADHD is related to the failures in regulating the dynamics of activity and communication between aforementioned large-scale networks. Additionally, CON's activity is shown to regulate the activity and FC of the DMN and FPNs (Di and Biswal, 2014; Menon and Uddin, 2010; Sevinc *et al.*, 2017). Additionally, previous research identified pronounced temporal fluctuations in the strength of FCs over time, mainly for the inter-network links connecting the DMN and FPNs (Zalesky *et al.*, 2014). Of note, ADHD subjects are shown to have a higher level of variability in their resting-state BOLD signals (Mowinckel *et al.*, 2017; Nomi

*et al.*, 2018). However, the critical role of the temporal dimension in the FC patterns of ADHD has previously not been adequately taken in to account.

In the context of the ADHD brain connectivity, both FCs within the DMN subsystems and between the DMN and cognitive control systems are of particular interest. In view of the foregoing, we aimed to propose a new FC analysis approach allowing us simultaneously assess the time-varying intra-DMN FCs as well as the time-varying FCs of the DMN with cognitive control networks (aka inter-DMN FCs), to get a complete picture of putative differences in the synergistic cooperation patterns of the DMN, in ADHD compared to controls. Particularly, we aimed to preserve the configuration of both intra- and inter-network FCs, unlike commonly used methods which reduce this pattern to one single measure representing network segregation.

#### *6.3.3.2 Methods*

We applied standard pre-processing steps to the resting-state fMRI data from 121 healthy controls and 40 subjects diagnosed with ADHD (Poldrack *et al.*, 2016). Then, the DMN, CON and FPNs were extracted by means of the ICA (Allen *et al.*, 2011; Calhoun *et al.*, 2001a) and their respective time-courses were detrended, despiked, and low-pass filtered. The identified ICA maps included the anterior and posterior subsystems of the DMN (aDMN and pDMN), and the posterolateral parietal subsystem of the DMN, centered at temporoparietal junction (TPJ), as well cognitive control related networks, including left and right FPNs (lFPN and rFPN) and the CON network. Next, we computed the instantaneous phase synchrony for each pair of ICA networks, since it provides single time-point resolution of FC, with no need for an arbitrary selection of time-window length contrary to correlation-based sliding window analysis. Subsequently, intra- and inter-network state-space trajectories were constructed for the DMN, in order to perform topological state-space analysis of DMN dynamics. In other words, for each individual, we had an intra-DMN trajectory in a 3d state-space, created from 3 FCs linking different DMN subsystems to each other, as well as an inter-DMN trajectory which was in a 9d state-space, formed by 9 FCs, linking the DMN to the cognitive control networks.

After we separately constructed the state-space trajectories for the intra-DMN and inter-DMN FCs, we computed their respective recurrence plots separately. Afterwards, we created the joint recurrence plot (Marwan *et al.*, 2007) from the recurrence plots computed independently for the 3d intra-DMN and the 9d inter-DMN trajectories. Recurrence plot enables us to visualize and also to get important insights into the time evolution of the trajectories, specifically in the case of high dimensional systems. By quantification of vertical/horizontal line structures in the resultant joint recurrence plot, we obtained laminarity and trapping time (Marwan *et al.*, 2007), which respectively indicate how often the system is trapped at particular states and the average time interval spent at those trapped states. Age, sex and FD were regressed out from the aforementioned measures and bootstrap resampling was employed to compare them between healthy and ADHD groups. Finally, resultant laminar states, which were each characterized by a 12d vector consisting of 12 FC measures (3 intra-

DMN FCs + 9 inter-DMN FCs) were concatenated across all subjects, in order to split connectivity vectors into k clusters. Hierarchical consensus clustering (Jeub *et al.*, 2018) allowed us to get the most stable partitions, with no need to an arbitrary choice of the exact number of clusters or even a threshold for consensus clustering. The hierarchical consensus clustering detected 3 clusters, in each of them the mean vector (centroid) serves as a prototype of a particular FC configuration, which we refer to as synergy. Finally, we investigated if the ADHD cohort differed in either the synergetic cooperation patterns, or their recruitment rate.

#### *6.3.3.3 Results*

We observed a significantly higher degree of laminarity and trapping time for the healthy compared with the ADHD cohort, suggesting that a lesser degree of stable cooperation patterns was found for the DMN in ADHD subjects. Accordingly, our analysis of the synergistic cooperation patterns between the DMN and cognitive control networks was focused on the time-intervals for which the configurations of both intra- and inter-DMN connections have jointly reached their steady states. We found three synergies, each of them providing us with detailed information regarding the relative values of 12 DMN-related FCs recruited in an almost invariable fashion for at least 4 seconds. We observed that 45% of the entire laminar states were classified as a synergy which was characterized by a marked decrease in the FC between the pDMN and the other two DMN sub-networks (aDMN and TPJ), but strong FC between the aDMN and TPJ. The other two synergies were respectively employed at 27% and 28% of the laminar states, one of them characterized by an overall strong within DMN FC, and the other one related to a noticeable disconnection of aDMN and TPJ.

Furthermore, we observed a significantly stronger recruitment rate for the second synergy in the healthy cohort as compared with ADHD group. Finally, we found that ADHD group mainly differed in the synergetic cooperation pattern (i.e., the topology of synergies) of the synergy specified with strong distinctive within-DMN coherence. In detail, this particular synergy involved weaker FC for the pDMN — lFPN, pDMN — CON and aDMN — CON network pairs, in the healthy cohort as compared to the ADHD group.

### 6.3.4 Study IV — Adaptive Frequency-based Modeling of Whole-brain Oscillations: Predicting Regional Vulnerability and Hazardousness Rates

#### *6.3.4.1 Aims*

Computational modeling of whole-brain oscillations allows us to address a broad range of questions regarding the interplay between the brain's structure and dynamics (Breakspear *et al.*, 2010; Fink, 2018; Roberts *et al.*, 2018), without any experimental complication. For example, it provides us with a platform to simulate the effect of different brain lesions (Aerts *et al.*, 2016; Alstott *et al.*, 2009; Deco *et al.*, 2018; Váša *et al.*, 2015) which even further improves our understanding of brain function. Modeling large-scale brain dynamics based on

the structural connectome has shown great promise in simulating BOLD signals with temporal co-activation patterns similar to the FC patterns observed in the empirical data during resting state (Cabral *et al.*, 2014; Deco *et al.*, 2017; Ritter *et al.*, 2013). On the other hand, previous studies have indicated an inherent dynamic nature for the co-activation patterns among distributed brain regions, with regard to the frequency spectrum of intrinsic brain oscillations (Chang and Glover, 2010; Yaesoubi *et al.*, 2015). Therefore, we aimed to introduce frequency dynamics into a system of coupled oscillators modeling brain dynamics. Subsequently, we intended to apply an *in silico* perturbation protocol to examine the effects of lesions on whole-brain co-activation patterns and to suggest a way to quantify local vulnerability and hazardousness of different brain regions/connections.

#### *6.3.4.2 Methods*

We used resting-state fMRI data from the Human Connectome 500 subject release (Smith et al., 2013; Van Essen et al., 2012). The data was minimally-preprocessed (Glasser et al., 2013; Smith et al., 2013; Van Essen et al., 2012). We performed some further preprocessings like despiking, removing nuisance signals (mean WM and CSF signals as well as global signal) and temporal filtering (Fukushima *et al.*, 2018). Moreover, cortical surface of T1-weighted images were parcellated into 68 anatomically segregated gyral-based regions (Desikan *et al.*, 2006). Moreover, streamline tractography was performed (Yeh *et al.*, 2010) using the diffusion-weighted MRI data (Glasser et al., 2013; Van Essen et al., 2012). Measures of streamline density were used for creating the structural connectome (Hagmann *et al.*, 2008; van den Heuvel and Sporns, 2011; van den Heuvel *et al.*, 2012).

Whole-brain network dynamics were modeled by the collective behavior of coupled local mean-field models which were interacting through the structural connectome (Breakspear, 2017; Cabral et al., 2014; Deco and Jirsa, 2012; Deco et al., 2009; Gollo et al., 2015; Honey et al., 2009, 2007). By introducing the frequency dynamics, we modified the set of differential equations associated with coupled Stuart-Landau oscillators which was previously suggested as a model of whole-brain dynamics (Deco *et al.*, 2017; Freyer *et al.*, 2012; Senden *et al.*, 2017). We estimated the optimal values for our suggested model parameters by maximizing the similarity between model-driven and empirical measures of FC.

Subsequently, we perturbed different brain regions by shifting the dynamic regime of the targeted brain region (characterized by the local bifurcation parameter) from the oscillatory to the noisy domain (Figure 10). Benefitting from graph-theory and machine learning algorithms, we further investigated the effects of perturbations. First, we investigated whole-brain network breakdown under random perturbations versus targeted attacks to the hub regions, via measuring the fraction of brain regions belonging to the largest connected component. Next, we computed relative changes in nodal strength and inter-module FCs, in response to distributed perturbations in the whole brain, as suggestive measures of local vulnerability. Finally, several FC-based measures were computed for the healthy brain model as well as 68 models of the impaired brain (68 whole brain model corresponding to the 68 simulated local perturbations), to create a 13-dimensional feature vector for every simulated

perturbed/unperturbed set of whole-brain signals. Every particular perturbed region is likely to cause a feature space divergence from the optimal point associated with the feature vector of unperturbed brain model. We introduced the level of induced distance in the feature space as a measure of regional hazardousness.

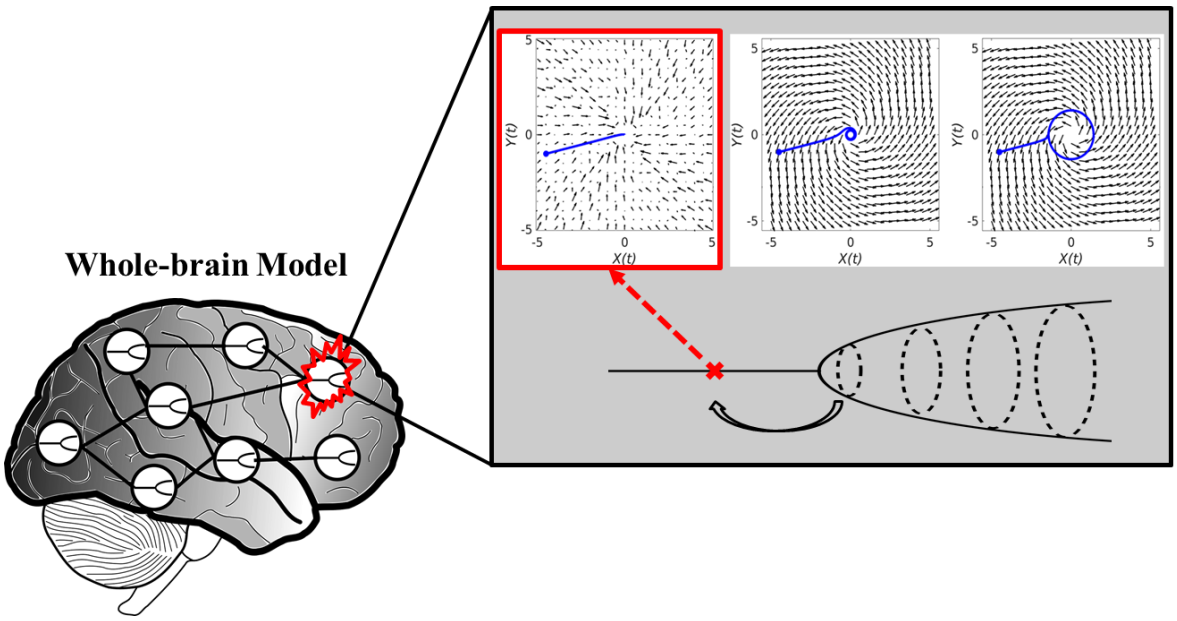


*Figure 10. Lesions were simulated by applying bifurcation-induced shifts in the characteristic behavior of the dynamical system.*

### *6.3.4.3 Results*

First, we provided some evidence that our frequency modulation-based model outperforms the previous model in the same class. Additionally, we observed that network fragmentation process resulting from random perturbations is gradual, whereas applying targeted attacks to the brain network cause abrupt network breakdown. Considering that hub-scores were calculated based on the preserved structural connectome and perturbations were simulated as a bifurcation-induced shift in the local dynamics, seeing a lower network tolerance for selective attacks may further validate our suggested model.

Further assessment of FC patterns after applying distributed perturbations showed that our brain is apparently more susceptible to hyper-connectivity than hypo-connectivity risks, particularly in the areas with high level of connectedness. We can see from the nodal vulnerability maps that the most noticeable hyper-connectivity risks are related to the regions in the default mode, salience, and control systems, namely the anterior-cingulate cortex, the inferior parietal cortex, the precuneus cortex, the PCC and the middle frontal gyrus. These results are similar to the previous literature on TBI (Hillary *et al.*, 2014; Iraji *et al.*, 2016; Mayer *et al.*, 2011). Vulnerability map of inter-system connections is also in line with different clinical studies on the effects of injury to brain networks.

Quantification of the hazard rates induced by primary failures of individual regions indicated the highest level of hazardousness for the superior parietal cortex, the right caudal middle frontal gyrus and the bilateral rostral middle frontal gyrus, as well as for the posteromedial subsystem of the DM network (particularly the precuneus cortex, the inferior parietal cortex and the isthmus – cingulate cortex). In addition, the entorhinal cortex in the limbic system was found to be a hazardous region. These findings substantiate the key role of these regions for global coordination of information transfer across the whole-brain network.

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